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(54) Title: POLYNUCLEOTIDES ENCODING NOVEL SECRETED PROTEINS

(57) Abstract: Isolated polynucleotides which have been derived from a variety of human tissue sources, and which encode novel secreted proteins, are provided. Also provided are methods for producing proteins using these polynucleotides, and the proteins so produced.

POLYNUCLEOTIDES ENCODING NOVEL SECRETED PROTEINS

RELATED APPLICATIONS

This application claims the benefit of prior-filed provisional patent application U.S. Serial No. 60/195,604 entitled "Polynucleotides Encoding Novel Secreted Proteins", filed April 6, 2000. The content of the above-referenced application is incorporated in its entirety.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Gargantuan efforts have been employed by various investigational projects to randomly sequence portions of naturally-occurring cDNAs. The rationale behind this approach to identification and sequencing genes is founded in two basic principles: (1) that transcribed cDNAs represent the product of the most important genes, namely those that are actually expressed *in vivo*, and (2) that efforts to sequence genes and other portions of the genome of target organisms which are not actually expressed wastes substantial effort on areas not likely to yield genetic information of therapeutic importance. Thus, the high-throughput sequencing efforts focus on only those portions of the genome which are expressed. The randomly produced cDNA sequences represent "expressed sequence tags" or "ESTs", which identify and can be used as probes for the longer, full-length cDNA or genomic sequence from which they were transcribed.

Although this "shortcut" approach to genomic sequencing presents savings of effort compared to sequencing of the complete genome, it still produced a vast array of ESTs which may not be directly useful as protein therapeutics. To date, the majority of protein-related drug discovery has focused on the use of secreted proteins to produce a desired therapeutic effect. Since the EST approach theoretically identifies all expressed proteins, it produces an EST library which contains a mixture of secreted proteins (such as hormones, cytokines and receptors) and non-secreted proteins (such as, for example, metabolic enzymes and cellular structural proteins), without identifying which ESTs correspond to proteins falling into either category. As a result, these methods are not optimally tailored to the needs of investigators searching for secreted proteins because

they must separate the secreted "wheat" from the non-secreted "chaff", wasting effort and resources in the process.

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning).

More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. Co-assigned U.S. Patent No. 5,536,637, which is incorporated herein by reference, provides methods for focusing genomic sequencing efforts on sequences encoding the secreted proteins which are of most interest for identification of protein therapeutics. The '637 patent discloses a "signal sequence trap" which selectively identifies partial sequences encoding secreted proteins, namely "secreted expressed sequence tags" or "sESTs". The sequences of these sESTs can be used to design probes to isolate the full-length cDNA clones that encode secreted proteins.

It is to these secreted proteins and the full-length polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

The present invention provides for full-length cDNAs isolated from a variety of human RNA/cDNA sources which encode novel secreted proteins.

In preferred embodiments, the present invention provides an isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of: SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID

NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208,

SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO:245, SEQ ID NO:246, SEQ ID NO:247, SEQ ID NO:248, SEQ ID NO:249, SEQ ID NO:250, SEQ ID NO:251, SEQ ID NO:252, SEQ ID NO:253, SEQ ID NO:254, SEQ ID NO:255, SEQ ID NO:256, SEQ ID NO:257, SEQ ID NO:258, SEQ ID NO:259, SEQ ID NO:260, SEQ ID NO:261, SEQ ID NO:262, SEQ ID NO:263, SEQ ID NO:264, SEQ ID NO:265, SEQ ID NO:266, SEQ ID NO:267, SEQ ID NO:268, SEQ ID NO:269, SEQ ID NO:270, SEQ ID NO:271, SEQ ID NO:272, SEQ ID NO:273, SEQ ID NO:274, SEQ ID NO:275, SEQ ID NO:276, SEQ ID NO:277, SEQ ID NO:278, SEQ ID NO:279, SEQ ID NO:280, SEQ ID NO:281, SEQ ID NO:282, SEQ ID NO:283, SEQ ID NO:284, SEQ ID NO:285, SEQ ID NO:286, SEQ ID NO:287, SEQ ID NO:288, SEQ ID NO:289, SEQ ID NO:290, SEQ ID NO:291, SEQ ID NO:292, SEQ ID NO:293, SEQ ID NO:294, SEQ ID NO:295, SEQ ID NO:296, SEQ ID NO:297, SEQ ID NO:298, SEQ ID NO:299, SEQ ID NO:300, SEQ ID NO:301, SEQ ID NO:302, SEQ ID NO:303, SEQ ID NO:304, SEQ ID NO:305, SEQ ID NO:306, SEQ ID NO:307, SEQ ID NO:308, SEQ ID NO:309, SEQ ID NO:310, SEQ ID NO:311, SEQ ID NO:312, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:315, SEQ ID NO:316, SEQ ID NO:317, SEQ ID NO:318, SEQ ID NO:319, SEQ ID NO:320, SEQ ID NO:321, SEQ ID NO:322, SEQ ID NO:323, SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:326, SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:329, SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334, SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO:338, SEQ ID NO:339, SEQ ID NO:340, SEQ ID NO:341, SEQ ID NO:342, SEQ ID NO:343, SEQ ID NO:344, SEQ ID NO:345, SEQ ID NO:346, SEQ ID NO:347, SEQ ID NO:348, SEQ ID NO:349, SEQ ID NO:350, SEQ ID NO:351, SEQ ID NO:352, SEQ ID NO:353, SEQ ID NO:354, SEQ ID NO:355, SEQ ID NO:356, SEQ ID NO:357, SEQ ID NO:358, SEQ ID NO:359, SEQ ID NO:360, SEQ ID NO:361, SEQ ID NO:362, SEQ ID NO:363, SEQ ID NO:364, SEQ ID NO:365, SEQ ID NO:366, SEQ ID NO:367, SEQ ID NO:368, SEQ ID NO:369, SEQ ID NO:370, SEQ ID NO:371, SEQ ID NO:372, SEQ ID NO:373, SEQ ID NO:374, SEQ ID NO:375, SEQ ID NO:376, SEQ ID NO:377, SEQ ID NO:378, SEQ ID NO:379, SEQ ID NO:380, SEQ ID

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or a complement of said sequence.

In other embodiments, the present invention provides an isolated polynucleotide consisting of a nucleotide sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID

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NO:605, SEQ ID NO:606, SEQ ID NO:607, SEQ ID NO:608, SEQ ID NO:609, SEQ ID NO:610, SEQ ID NO:611, SEQ ID NO:612, SEQ ID NO:613, SEQ ID NO:614, SEQ ID NO:615, SEQ ID NO:616, SEQ ID NO:617, SEQ ID NO:618, SEQ ID NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, SEQ ID NO:623, SEQ ID NO:624, SEQ ID NO:625;

or a complement of said sequence.

In further embodiments, the present invention provides an isolated polynucleotide consisting essentially of a nucleotide sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138,

SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO:245, SEQ ID NO:246, SEQ ID NO:247, SEQ ID NO:248, SEQ ID NO:249, SEQ ID NO:250, SEQ ID NO:251, SEQ ID NO:252, SEQ ID NO:253, SEQ ID NO:254, SEQ ID NO:255, SEQ ID NO:256, SEQ ID NO:257, SEQ ID NO:258, SEQ ID NO:259, SEQ ID NO:260, SEQ ID NO:261, SEQ ID NO:262, SEQ ID NO:263, SEQ ID NO:264, SEQ ID NO:265, SEQ ID NO:266, SEQ ID NO:267, SEQ ID NO:268, SEQ ID NO:269, SEQ ID NO:270, SEQ ID NO:271, SEQ ID NO:272, SEQ ID NO:273, SEQ ID NO:274, SEQ ID NO:275, SEQ ID NO:276, SEQ ID NO:277, SEQ ID NO:278, SEQ ID NO:279, SEQ ID NO:280, SEQ ID NO:281, SEQ ID NO:282, SEQ ID NO:283, SEQ ID NO:284, SEQ ID NO:285, SEQ ID NO:286, SEQ ID NO:287, SEQ ID NO:288, SEQ ID NO:289, SEQ ID NO:290, SEQ ID NO:291, SEQ ID NO:292, SEQ ID NO:293, SEQ ID NO:294, SEQ ID NO:295, SEQ ID NO:296, SEQ ID NO:297, SEQ ID NO:298, SEQ ID NO:299, SEQ ID NO:300, SEQ ID NO:301, SEQ ID NO:302, SEQ ID NO:303, SEQ ID NO:304, SEQ ID NO:305, SEQ ID NO:306, SEQ ID NO:307, SEQ ID NO:308, SEQ ID NO:309, SEQ ID NO:310, SEQ ID

NO:311, SEQ ID NO:312, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:315, SEQ ID NO:316, SEQ ID NO:317, SEQ ID NO:318, SEQ ID NO:319, SEQ ID NO:320, SEQ ID NO:321, SEQ ID NO:322, SEQ ID NO:323, SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:326, SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:329, SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334, SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO:338, SEQ ID NO:339, SEQ ID NO:340, SEQ ID NO:341, SEQ ID NO:342, SEQ ID NO:343, SEQ ID NO:344, SEQ ID NO:345, SEQ ID NO:346, SEQ ID NO:347, SEQ ID NO:348, SEQ ID NO:349, SEQ ID NO:350, SEQ ID NO:351, SEQ ID NO:352, SEQ ID NO:353, SEQ ID NO:354, SEQ ID NO:355, SEQ ID NO:356, SEQ ID NO:357, SEQ ID NO:358, SEQ ID NO:359, SEQ ID NO:360, SEQ ID NO:361, SEQ ID NO:362, SEQ ID NO:363, SEQ ID NO:364, SEQ ID NO:365, SEQ ID NO:366, SEQ ID NO:367, SEQ ID NO:368, SEQ ID NO:369, SEQ ID NO:370, SEQ ID NO:371, SEQ ID NO:372, SEQ ID NO:373, SEQ ID NO:374, SEQ ID NO:375, SEQ ID NO:376, SEQ ID NO:377, SEQ ID NO:378, SEQ ID NO:379, SEQ ID NO:380, SEQ ID NO:381, SEQ ID NO:382, SEQ ID NO:383, SEQ ID NO:384, SEQ ID NO:385, SEQ ID NO:386, SEQ ID NO:387, SEQ ID NO:388, SEQ ID NO:389, SEQ ID NO:390, SEQ ID NO:391, SEQ ID NO:392, SEQ ID NO:393, SEQ ID NO:394, SEQ ID NO:395, SEQ ID NO:396, SEQ ID NO:397, SEQ ID NO:398, SEQ ID NO:399, SEQ ID NO:400, SEQ ID NO:401, SEQ ID NO:402, SEQ ID NO:403, SEQ ID NO:404, SEQ ID NO:405, SEQ ID NO:406, SEQ ID NO:407, SEQ ID NO:408, SEQ ID NO:409, SEQ ID NO:410, SEQ ID NO:411, SEQ ID NO:412, SEQ ID NO:413, SEQ ID NO:414, SEQ ID NO:415, SEQ ID NO:416, SEQ ID NO:417, SEQ ID NO:418, SEQ ID NO:419, SEQ ID NO:420, SEQ ID NO:421, SEQ ID NO:422, SEQ ID NO:423, SEQ ID NO:424, SEQ ID NO:425, SEQ ID NO:426, SEQ ID NO:427, SEQ ID NO:428, SEQ ID NO:429, SEQ ID NO:430, SEQ ID NO:431, SEQ ID NO:432, SEQ ID NO:433, SEQ ID NO:434, SEQ ID NO:435, SEQ ID NO:436, SEQ ID NO:437, SEQ ID NO:438, SEQ ID NO:439, SEQ ID NO:440, SEQ ID NO:441, SEQ ID NO:442, SEQ ID NO:443, SEQ ID NO:444, SEQ ID NO:445, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:449, SEQ ID NO:450, SEQ ID NO:451, SEQ ID NO:452, SEQ ID NO:453, SEQ ID NO:454, SEQ ID NO:455, SEQ ID NO:456, SEQ ID NO:457, SEQ ID NO:458, SEQ ID NO:459, SEQ ID NO:460, SEQ ID NO:461, SEQ ID NO:462, SEQ ID NO:463, SEQ ID NO:464, SEQ ID NO:465, SEQ ID NO:466, SEQ ID NO:467, SEQ ID NO:468, SEQ ID NO:469, SEQ ID NO:470, SEQ ID NO:471, SEQ ID NO:472, SEQ ID NO:473, SEQ ID NO:474, SEQ ID NO:475, SEQ ID NO:476, SEQ ID NO:477, SEQ ID NO:478, SEQ ID NO:479, SEQ ID NO:480, SEQ ID NO:481, SEQ ID NO:482, SEQ ID NO:483, SEQ

ID NO:484, SEQ ID NO:485, SEQ ID NO:486, SEQ ID NO:487, SEQ ID NO:488, SEQ ID NO:489, SEQ ID NO:490, SEQ ID NO:491, SEQ ID NO:492, SEQ ID NO:493, SEQ ID NO:494, SEQ ID NO:495, SEQ ID NO:496, SEQ ID NO:497, SEQ ID NO:498, SEQ ID NO:499, SEQ ID NO:500, SEQ ID NO:501, SEQ ID NO:502, SEQ ID NO:503, SEQ ID NO:504, SEQ ID NO:505, SEQ ID NO:506, SEQ ID NO:507, SEQ ID NO:508, SEQ ID NO:509, SEQ ID NO:510, SEQ ID NO:511, SEQ ID NO:512, SEQ ID NO:513, SEQ ID NO:514, SEQ ID NO:515, SEQ ID NO:516, SEQ ID NO:517, SEQ ID NO:518, SEQ ID NO:519, SEQ ID NO:520, SEQ ID NO:521, SEQ ID NO:522, SEQ ID NO:523, SEQ ID NO:524, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:540, SEQ ID NO:541, SEQ ID NO:542, SEQ ID NO:543, SEQ ID NO:544, SEQ ID NO:545, SEQ ID NO:546, SEQ ID NO:547, SEQ ID NO:548, SEQ ID NO:549, SEQ ID NO:550, SEQ ID NO:551, SEQ ID NO:552, SEQ ID NO:553, SEQ ID NO:554, SEQ ID NO:555, SEQ ID NO:556, SEQ ID NO:557, SEQ ID NO:558, SEQ ID NO:559, SEQ ID NO:560, SEQ ID NO:561, SEQ ID NO:562, SEQ ID NO:563, SEQ ID NO:564, SEQ ID NO:565, SEQ ID NO:566, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:569, SEQ ID NO:570, SEQ ID NO:571, SEQ ID NO:572, SEQ ID NO:573, SEQ ID NO:574, SEQ ID NO:575, SEQ ID NO:576, SEQ ID NO:577, SEQ ID NO:578, SEQ ID NO:579, SEQ ID NO:580, SEQ ID NO:581, SEQ ID NO:582, SEQ ID NO:583, SEQ ID NO:584, SEQ ID NO:585, SEQ ID NO:586, SEQ ID NO:587, SEQ ID NO:588, SEQ ID NO:589, SEQ ID NO:590, SEQ ID NO:591, SEQ ID NO:592, SEQ ID NO:593, SEQ ID NO:594, SEQ ID NO:595, SEQ ID NO:596, SEQ ID NO:597, SEQ ID NO:598, SEQ ID NO:599, SEQ ID NO:600, SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:603, SEQ ID NO:604, SEQ ID NO:605, SEQ ID NO:606, SEQ ID NO:607, SEQ ID NO:608, SEQ ID NO:609, SEQ ID NO:610, SEQ ID NO:611, SEQ ID NO:612, SEQ ID NO:613, SEQ ID NO:614, SEQ ID NO:615, SEQ ID NO:616, SEQ ID NO:617, SEQ ID NO:618, SEQ ID NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, SEQ ID NO:623, SEQ ID NO:624, SEQ ID NO:625;

or a complement of said sequence.

In yet other embodiments, the present invention provides an isolated polynucleotide comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID

NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ

ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO:245, SEQ ID NO:246, SEQ ID NO:247, SEQ ID NO:248, SEQ ID NO:249, SEQ ID NO:250, SEQ ID NO:251, SEQ ID NO:252, SEQ ID NO:253, SEQ ID NO:254, SEQ ID NO:255, SEQ ID NO:256, SEQ ID NO:257, SEQ ID NO:258, SEQ ID NO:259, SEQ ID NO:260, SEQ ID NO:261, SEQ ID NO:262, SEQ ID NO:263, SEQ ID NO:264, SEQ ID NO:265, SEQ ID NO:266, SEQ ID NO:267, SEQ ID NO:268, SEQ ID NO:269, SEQ ID NO:270, SEQ ID NO:271, SEQ ID NO:272, SEQ ID NO:273, SEQ ID NO:274, SEQ ID NO:275, SEQ ID NO:276, SEQ ID NO:277, SEQ ID NO:278, SEQ ID NO:279, SEQ ID NO:280, SEQ ID NO:281, SEQ ID NO:282, SEQ ID NO:283, SEQ ID NO:284, SEQ ID NO:285, SEQ ID NO:286, SEQ ID NO:287, SEQ ID NO:288, SEQ ID NO:289, SEQ ID NO:290, SEQ ID NO:291, SEQ ID NO:292, SEQ ID NO:293, SEQ ID NO:294, SEQ ID NO:295, SEQ ID NO:296, SEQ ID NO:297, SEQ ID NO:298, SEQ ID NO:299, SEQ ID NO:300, SEQ ID NO:301, SEQ ID NO:302, SEQ ID NO:303, SEQ ID NO:304, SEQ ID NO:305, SEQ ID NO:306, SEQ ID NO:307, SEQ ID NO:308, SEQ ID NO:309, SEQ ID NO:310, SEQ ID NO:311, SEQ ID NO:312, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:315, SEQ ID NO:316, SEQ ID NO:317, SEQ ID NO:318, SEQ ID NO:319, SEQ ID NO:320, SEQ ID NO:321, SEQ ID NO:322, SEQ ID NO:323, SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:326, SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:329, SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334, SEQ ID NO:335, SEQ ID NO:336, SEQ ID NO:337, SEQ ID NO:338, SEQ ID NO:339, SEQ ID NO:340, SEQ ID NO:341, SEQ ID NO:342, SEQ ID NO:343, SEQ ID NO:344, SEQ ID NO:345, SEQ ID NO:346, SEQ ID NO:347, SEQ ID NO:348, SEQ ID NO:349, SEQ ID NO:350, SEQ ID NO:351, SEQ ID NO:352, SEQ ID NO:353, SEQ ID NO:354, SEQ ID NO:355, SEQ ID NO:356, SEQ ID NO:357, SEQ ID NO:358, SEQ ID NO:359, SEQ ID NO:360, SEQ ID NO:361, SEQ ID NO:362,

SEQ ID NO:363, SEQ ID NO:364, SEQ ID NO:365, SEQ ID NO:366, SEQ ID NO:367, SEQ ID NO:368, SEQ ID NO:369, SEQ ID NO:370, SEQ ID NO:371, SEQ ID NO:372, SEQ ID NO:373, SEQ ID NO:374, SEQ ID NO:375, SEQ ID NO:376, SEQ ID NO:377, SEQ ID NO:378, SEQ ID NO:379, SEQ ID NO:380, SEQ ID NO:381, SEQ ID NO:382, SEQ ID NO:383, SEQ ID NO:384, SEQ ID NO:385, SEQ ID NO:386, SEQ ID NO:387, SEQ ID NO:388, SEQ ID NO:389, SEQ ID NO:390, SEQ ID NO:391, SEQ ID NO:392, SEQ ID NO:393, SEQ ID NO:394, SEQ ID NO:395, SEQ ID NO:396, SEQ ID NO:397, SEQ ID NO:398, SEQ ID NO:399, SEQ ID NO:400, SEQ ID NO:401, SEQ ID NO:402, SEQ ID NO:403, SEQ ID NO:404, SEQ ID NO:405, SEQ ID NO:406, SEQ ID NO:407, SEQ ID NO:408, SEQ ID NO:409, SEQ ID NO:410, SEQ ID NO:411, SEQ ID NO:412, SEQ ID NO:413, SEQ ID NO:414, SEQ ID NO:415, SEQ ID NO:416, SEQ ID NO:417, SEQ ID NO:418, SEQ ID NO:419, SEQ ID NO:420, SEQ ID NO:421, SEQ ID NO:422, SEQ ID NO:423, SEQ ID NO:424, SEQ ID NO:425, SEQ ID NO:426, SEQ ID NO:427, SEQ ID NO:428, SEQ ID NO:429, SEQ ID NO:430, SEQ ID NO:431, SEQ ID NO:432, SEQ ID NO:433, SEQ ID NO:434, SEQ ID NO:435, SEQ ID NO:436, SEQ ID NO:437, SEQ ID NO:438, SEQ ID NO:439, SEQ ID NO:440, SEQ ID NO:441, SEQ ID NO:442, SEQ ID NO:443, SEQ ID NO:444, SEQ ID NO:445, SEQ ID NO:446, SEQ ID NO:447, SEQ ID NO:448, SEQ ID NO:449, SEQ ID NO:450, SEQ ID NO:451, SEQ ID NO:452, SEQ ID NO:453, SEQ ID NO:454, SEQ ID NO:455, SEQ ID NO:456, SEQ ID NO:457, SEQ ID NO:458, SEQ ID NO:459, SEQ ID NO:460, SEQ ID NO:461, SEQ ID NO:462, SEQ ID NO:463, SEQ ID NO:464, SEQ ID NO:465, SEQ ID NO:466, SEQ ID NO:467, SEQ ID NO:468, SEQ ID NO:469, SEQ ID NO:470, SEQ ID NO:471, SEQ ID NO:472, SEQ ID NO:473, SEQ ID NO:474, SEQ ID NO:475, SEQ ID NO:476, SEQ ID NO:477, SEQ ID NO:478, SEQ ID NO:479, SEQ ID NO:480, SEQ ID NO:481, SEQ ID NO:482, SEQ ID NO:483, SEQ ID NO:484, SEQ ID NO:485, SEQ ID NO:486, SEQ ID NO:487, SEQ ID NO:488, SEQ ID NO:489, SEQ ID NO:490, SEQ ID NO:491, SEQ ID NO:492, SEQ ID NO:493, SEQ ID NO:494, SEQ ID NO:495, SEQ ID NO:496, SEQ ID NO:497, SEQ ID NO:498, SEQ ID NO:499, SEQ ID NO:500, SEQ ID NO:501, SEQ ID NO:502, SEQ ID NO:503, SEQ ID NO:504, SEQ ID NO:505, SEQ ID NO:506, SEQ ID NO:507, SEQ ID NO:508, SEQ ID NO:509, SEQ ID NO:510, SEQ ID NO:511, SEQ ID NO:512, SEQ ID NO:513, SEQ ID NO:514, SEQ ID NO:515, SEQ ID NO:516, SEQ ID NO:517, SEQ ID NO:518, SEQ ID NO:519, SEQ ID NO:520, SEQ ID NO:521, SEQ ID NO:522, SEQ ID NO:523, SEQ ID NO:524, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID

NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:540, SEQ ID NO:541, SEQ ID NO:542, SEQ ID NO:543, SEQ ID NO:544, SEQ ID NO:545, SEQ ID NO:546, SEQ ID NO:547, SEQ ID NO:548, SEQ ID NO:549, SEQ ID NO:550, SEQ ID NO:551, SEQ ID NO:552, SEQ ID NO:553, SEQ ID NO:554, SEQ ID NO:555, SEQ ID NO:556, SEQ ID NO:557, SEQ ID NO:558, SEQ ID NO:559, SEQ ID NO:560, SEQ ID NO:561, SEQ ID NO:562, SEQ ID NO:563, SEQ ID NO:564, SEQ ID NO:565, SEQ ID NO:566, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:569, SEQ ID NO:570, SEQ ID NO:571, SEQ ID NO:572, SEQ ID NO:573, SEQ ID NO:574, SEQ ID NO:575, SEQ ID NO:576, SEQ ID NO:577, SEQ ID NO:578, SEQ ID NO:579, SEQ ID NO:580, SEQ ID NO:581, SEQ ID NO:582, SEQ ID NO:583, SEQ ID NO:584, SEQ ID NO:585, SEQ ID NO:586, SEQ ID NO:587, SEQ ID NO:588, SEQ ID NO:589, SEQ ID NO:590, SEQ ID NO:591, SEQ ID NO:592, SEQ ID NO:593, SEQ ID NO:594, SEQ ID NO:595, SEQ ID NO:596, SEQ ID NO:597, SEQ ID NO:598, SEQ ID NO:599, SEQ ID NO:600, SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:603, SEQ ID NO:604, SEQ ID NO:605, SEQ ID NO:606, SEQ ID NO:607, SEQ ID NO:608, SEQ ID NO:609, SEQ ID NO:610, SEQ ID NO:611, SEQ ID NO:612, SEQ ID NO:613, SEQ ID NO:614, SEQ ID NO:615, SEQ ID NO:616, SEQ ID NO:617, SEQ ID NO:618, SEQ ID NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, SEQ ID NO:623, SEQ ID NO:624, SEQ ID NO:625;

or to a complement of said sequence.

The invention also provides for proteins encoded by the above-described polynucleotides. In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions. Also provided by the present invention are organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

Processes are also provided for producing a protein, which comprise:

- (a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and
- (b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention, and/or a polynucleotide of the present invention, and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

The nucleotide sequences of the isolated cDNAs of the present invention are reported in the Sequence Listing below. Table 2 lists the "Clone ID Nos." assigned by applicants to each SEQ ID NO: in the Sequence Listing.

Table 2

Each pair of entries in this table consists of the SEQ ID NO (e.g., 1, 2, etc.) followed by the Clone ID No. for such sequence (e.g., YI116_1, YI117_1, etc.).

1	YI116_1	201	YJA47_1	401	YK297_1	601	YL210_1
2	YI117_1	202	YK102_1	402	YK298_1	602	YL211_1
3	YI118_1	203	YK103_1	403	YK299_1	603	YL212_1
4	YI119_1	204	YK104_1	404	YK29_1	604	YL213_1
5	YI120_1	205	YK105_1	405	YK2_1	605	YL214_1
6	YI122_1	206	YK106_1	406	YK300_1	606	YL215_1
7	YI123_1	207	YK107_1	407	YK301_1	607	YL216_1
8	YI124_1	208	YK108_1	408	YK302_1	608	YL217_1
9	YI125_1	209	YK109_1	409	YK303_1	609	YL218_1
10	YI126_1	210	YK10_1	410	YK304_1	610	YL219_1
11	YI127_1	211	YK110_1	411	YK305_1	611	YL21_1
12	YI128_1	212	YK111_1	412	YK306_1	612	YL220_1
13	YI129_1	213	YK112_1	413	YK307_1	613	YL221_1
14	YI130_1	214	YK113_1	414	YK308_1	614	YL222_1
15	YI131_1	215	YK114_1	415	YK309_1	615	YL223_1
16	YI132_1	216	YK115_1	416	YK30_1	616	YL224_1
17	YI133_1	217	YK116_1	417	YK310_1	617	YL225_1
18	YI135_1	218	YK117_1	418	YK311_1	618	YL226_1
19	YI136_1	219	YK118_1	419	YK312_1	619	YL227_1
20	YI137_1	220	YK119_1	420	YK313_1	620	YL228_1
21	YI138_1	221	YK11_1	421	YK316_1	621	YL229_1

22	YI139_1	222	YK120_1	422	YK31_1	622	YL22_1
23	YI13_1	223	YK121_1	423	YK320_1	623	YL230_1
24	YI140_1	224	YK122_1	424	YK326_1	624	YL231_1
25	YI141_1	225	YK123_1	425	YK32_1	625	YL232_1
26	YI142_1	226	YK124_1	426	YK33_1		
27	YI143_1	227	YK126_1	427	YK34_1		
28	YI144_1	228	YK127_1	428	YK35_1		
29	YI145_1	229	YK128_1	429	YK36_1		
30	YI146_1	230	YK129_1	430	YK37_1		
31	YI147_1	231	YK12_1	431	YK3_1		
32	YI148_1	232	YK130_1	432	YK40_1		
33	YI149_1	233	YK131_1	433	YK41_1		
34	YI14_1	234	YK132_1	434	YK42_1		
35	YI150_1	235	YK133_1	435	YK43_1		
36	YI151_1	236	YK134_1	436	YK44_1		
37	YI152_1	237	YK135_1	437	YK45_1		
38	YI153_1	238	YK136_1	438	YK47_1		
39	YI154_1	239	YK137_1	439	YK48_1		
40	YI155_1	240	YK138_1	440	YK49_1		
41	YI156_1	241	YK139_1	441	YK4_1		
42	YI157_1	242	YK13_1	442	YK50_1		
43	YI158_1	243	YK140_1	443	YK52_1		
44	YI159_1	244	YK141_1	444	YK53_1		
45	YI160_1	245	YK142_1	445	YK54_1		
46	YI161_1	246	YK144_1	446	YK55_1		
47	YI162_1	247	YK145_1	447	YK56_1		
48	YI163_1	248	YK146_1	448	YK57_1		
49	YI164_1	249	YK147_1	449	YK58_1		
50	YI165_1	250	YK148_1	450	YK5_1		
51	YI166_1	251	YK149_1	451	YK60_1		
52	YI167_1	252	YK150_1	452	YK63_1		
53	YI168_1	253	YK151_1	453	YK65_1		
54	YI169_1	254	YK152_1	454	YK66_1		
55	YI170_1	255	YK153_1	455	YK68_1		
56	YI171_1	256	YK154_1	456	YK69_1		
57	YI172_1	257	YK155_1	457	YK6_1		
58	YI173_1	258	YK157_1	458	YK70_1		

59	YI174_1	259	YK158_1	459	YK71_1
60	YI175_1	260	YK159_1	460	YK72_1
61	YI176_1	261	YK15_1	461	YK73_1
62	YI177_1	262	YK160_1	462	YK75_1
63	YI179_1	263	YK161_1	463	YK77_1
64	YI180_1	264	YK162_1	464	YK79_1
65	YI181_1	265	YK163_1	465	YK7_1
66	YI182_1	266	YK164_1	466	YK80_1
67	YI183_1	267	YK165_1	467	YK81_1
68	YI185_1	268	YK166_1	468	YK83_1
69	YI186_1	269	YK167_1	469	YK85_1
70	YI188_1	270	YK168_1	470	YK86_1
71	YI189_1	271	YK169_1	471	YK87_1
72	YI19_1	272	YK16_1	472	YK88_1
73	YI20_1	273	YK170_1	473	YK8_1
74	YI21_1	274	YK171_1	474	YK90_1
75	YI22_1	275	YK172_1	475	YK92_1
76	YI23_1	276	YK175_1	476	YK93_1
77	YI24_1	277	YK176_1	477	YK94_1
78	YI25_1	278	YK177_1	478	YK95_1
79	YI26_1	279	YK178_1	479	YK96_1
80	YI27_1	280	YK179_1	480	YK97_1
81	YI28_1	281	YK17_1	481	YK98_1
82	YI29_1	282	YK180_1	482	YK99_1
83	YI2_1	283	YK181_1	483	YK9_1
84	YI30_1	284	YK182_1	484	YKA1_1
85	YI33_1	285	YK183_1	485	YKA2_1
86	YI34_1	286	YK184_1	486	YKA3_1
87	YI36_1	287	YK185_1	487	YL100_1
88	YI37_1	288	YK186_1	488	YL101_1
89	YI38_1	289	YK187_1	489	YL102_1
90	YI39_1	290	YK188_1	490	YL103_1
91	YI40_1	291	YK189_1	491	YL104_1
92	YI41_1	292	YK18_1	492	YL105_1
93	YI42_1	293	YK191_1	493	YL106_1
94	YI43_1	294	YK192_1	494	YL107_1
95	YI46_1	295	YK193_1	495	YL108_1

96	YI47_1	296	YK194_1	496	YL109_1
97	YI48_1	297	YK195_1	497	YL10_1
98	YI49_1	298	YK196_1	498	YL110_1
99	YI50_1	299	YK197_1	499	YL111_1
100	YI51_1	300	YK198_1	500	YL112_1
101	YI53_1	301	YK19_1	501	YL113_1
102	YI54_1	302	YK200_1	502	YL114_1
103	YI55_1	303	YK201_1	503	YL115_1
104	YI56_1	304	YK202_1	504	YL116_1
105	YI57_1	305	YK203_1	505	YL117_1
106	YI58_1	306	YK205_1	506	YL118_1
107	YI59_1	307	YK206_1	507	YL119_1
108	YI5_1	308	YK207_1	508	YL11_1
109	YI60_1	309	YK208_1	509	YL120_1
110	YI61_1	310	YK209_1	510	YL121_1
111	YI63_1	311	YK20_1	511	YL122_1
112	YI64_1	312	YK210_1	512	YL123_1
113	YI65_1	313	YK211_1	513	YL124_1
114	YI66_1	314	YK212_1	514	YL125_1
115	YI67_1	315	YK213_1	515	YL126_1
116	YI69_1	316	YK214_1	516	YL127_1
117	YI70_1	317	YK215_1	517	YL128_1
118	YI71_1	318	YK216_1	518	YL129_1
119	YI72_1	319	YK217_1	519	YL12_1
120	YI73_1	320	YK218_1	520	YL130_1
121	YI74_1	321	YK219_1	521	YL131_1
122	YI76_1	322	YK21_1	522	YL132_1
123	YI77_1	323	YK220_1	523	YL133_1
124	YI79_1	324	YK221_1	524	YL134_1
125	YI80_1	325	YK222_1	525	YL135_1
126	YI81_1	326	YK223_1	526	YL136_1
127	YI82_1	327	YK225_1	527	YL137_1
128	YI84_1	328	YK226_1	528	YL138_1
129	YI85_1	329	YK227_1	529	YL139_1
130	YI86_1	330	YK228_1	530	YL13_1
131	YI87_1	331	YK229_1	531	YL140_1
132	YI88_1	332	YK22_1	532	YL141_1

133	YI89_1	333	YK230_1	533	YL142_1
134	YI90_1	334	YK231_1	534	YL143_1
135	YI91_1	335	YK232_1	535	YL144_1
136	YI92_1	336	YK233_1	536	YL145_1
137	YI93_1	337	YK234_1	537	YL146_1
138	YI94_1	338	YK235_1	538	YL147_1
139	YI95_1	339	YK236_1	539	YL148_1
140	YI96_1	340	YK237_1	540	YL149_1
141	YI97_1	341	YK238_1	541	YL150_1
142	YI98_1	342	YK239_1	542	YL151_1
143	YI99_1	343	YK240_1	543	YL152_1
144	YIA17_1	344	YK241_1	544	YL153_1
145	YIA18_1	345	YK242_1	545	YL154_1
146	YIA19_1	346	YK243_1	546	YL155_1
147	YIA1_1	347	YK244_1	547	YL156_1
148	YIA20_1	348	YK245_1	548	YL157_1
149	YIA21_1	349	YK246_1	549	YL158_1
150	YJ11_1	350	YK247_1	550	YL15_1
151	YJ12_1	351	YK248_1	551	YL160_1
152	YJ13_1	352	YK249_1	552	YL161_1
153	YJ14_1	353	YK24_1	553	YL163_1
154	YJ15_1	354	YK250_1	554	YL164_1
155	YJ16_1	355	YK252_1	555	YL165_1
156	YJ17_1	356	YK253_1	556	YL166_1
157	YJ18_1	357	YK254_1	557	YL167_1
158	YJ19_1	358	YK255_1	558	YL168_1
159	YJ1_1	359	YK256_1	559	YL169_1
160	YJ20_1	360	YK257_1	560	YL16_1
161	YJ21_1	361	YK258_1	561	YL170_1
162	YJ22_1	362	YK259_1	562	YL171_1
163	YJ24_1	363	YK260_1	563	YL172_1
164	YJ25_1	364	YK262_1	564	YL173_1
165	YJ26_1	365	YK264_1	565	YL174_1
166	YJ27_1	366	YK265_1	566	YL175_1
167	YJ2_1	367	YK266_1	567	YL176_1
168	YJ30_1	368	YK267_1	568	YL177_1
169	YJ31_1	369	YK268_1	569	YL178_1

170	YJ34_1	370	YK269_1	570	YL17_1
171	YJ35_1	371	YK26_1	571	YL180_1
172	YJ36_1	372	YK270_1	572	YL181_1
173	YJ37_1	373	YK271_1	573	YL182_1
174	YJ38_1	374	YK272_1	574	YL184_1
175	YJ4_1	375	YK273_1	575	YL186_1
176	YJ8_1	376	YK274_1	576	YL187_1
177	YJ9_1	377	YK275_1	577	YL188_1
178	YJA1_1	378	YK276_1	578	YL189_1
179	YJA23_1	379	YK277_1	579	YL190_1
180	YJA25_1	380	YK278_1	580	YL191_1
181	YJA26_1	381	YK279_1	581	YL192_1
182	YJA28_1	382	YK27_1	582	YL193_1
183	YJA29_1	383	YK280_1	583	YL195_1
184	YJA30_1	384	YK281_1	584	YL196_1
185	YJA31_1	385	YK282_1	585	YL197_1
186	YJA32_1	386	YK283_1	586	YL198_1
187	YJA33_1	387	YK284_1	587	YL199_1
188	YJA34_1	388	YK285_1	588	YL19_1
189	YJA35_1	389	YK286_1	589	YL1_1
190	YJA36_1	390	YK287_1	590	YL200_1
191	YJA37_1	391	YK288_1	591	YL201_1
192	YJA38_1	392	YK289_1	592	YL202_1
193	YJA39_1	393	YK28_1	593	YL203_1
194	YJA40_1	394	YK290_1	594	YL204_1
195	YJA41_1	395	YK291_1	595	YL205_1
196	YJA42_1	396	YK292_1	596	YL206_1
197	YJA43_1	397	YK293_1	597	YL207_1
198	YJA44_1	398	YK294_1	598	YL208_1
199	YJA45_1	399	YK295_1	599	YL209_1
200	YJA46_1	400	YK296_1	600	YL20_1

The "Clone ID No." for a particular clone consists of one or two letters followed by a number. The letters designate the tissue source from which the cDNA for that clone was isolated, and these sources are listed in Table 3 below.

TABLE 3

<u>Sel.</u>	<u>Species</u>	<u>Stage</u>	<u>Tissue</u>	<u>Cell Type</u>	<u>Treatment</u>
YI	Human	Adult	Brain	N/A	None
YIA	Human	Adult	Thymus	N/A	None
YJ	Human	Adult	Kidney	293 embryonal carcinoma line	None
YJA	Human	Adult	Retina	WERI-Rb1 retinoblastoma line	None
YK	Human	Adult	Thymus	N/A	None
YKA	Human	Adult	Fibrosarcoma	Epithelial HT-1080 line	None
YL	Human	Adult	Spleen	N/A	None

Thus, the tissue source for a particular cDNA sequence can be identified in Table 3 by the one and two letter designations used in the relevant "Clone ID No." in Table 2. For example, a cDNA clone designated as "YI116_1" would have been isolated from a human adult brain library (i.e., selection "YI") as indicated in Table 3.

As used herein, "polynucleotide" includes single- and double-stranded RNAs, DNAs and RNA:DNA hybrids.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g., receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The

mature form(s) of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence(s) of the mature form(s) of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

The chromosomal location corresponding to the polynucleotide sequences disclosed herein may also be determined, for example by hybridizing appropriately labeled polynucleotides of the present invention to chromosomes *in situ*. It may also be possible to determine the corresponding chromosomal location for a disclosed polynucleotide by identifying significantly similar nucleotide sequences in public databases, such as expressed sequence tags (ESTs), that have already been mapped to particular chromosomal locations. For at least some of the polynucleotide sequences disclosed herein, public database sequences having at least some similarity to the polynucleotide of the present invention have been listed by database accession number. Searches using the GenBank accession numbers of these public database sequences can then be performed at an Internet site provided by the National Center for Biotechnology Information having the address www.ncbi.nlm.nih.gov/UniGene, in order to identify "UniGene clusters" of overlapping sequences. Many of the "UniGene clusters" so identified will already have been mapped to particular chromosomal sites.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* 15(7): 250- 254; Lavarosky *et al.*,

1997, *Biochem. Mol. Med.* 62(1): 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* 14(9): 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90(16): 7431-7435; Clark *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614,396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by

comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

In particular, sequence identity may be determined using WU-BLAST (Washington University BLAST) version 2.0 software, which builds upon WU-BLAST version 1.4, which in turn is based on the public domain NCBI-BLAST version 1.4 (Altschul and Gish, 1996, Local alignment statistics, Doolittle *ed.*, *Methods in Enzymology* 266: 460-480; Altschul *et al.*, 1990, Basic local alignment search tool, *Journal of Molecular Biology* 215: 403-410; Gish and States, 1993, Identification of protein coding regions by database similarity search, *Nature Genetics* 3: 266-272; Karlin and Altschul, 1993, Applications and statistics for multiple high-scoring segments in molecular sequences, *Proc. Natl. Acad. Sci. USA* 90: 5873-5877; all of which are incorporated by reference herein). WU-BLAST version 2.0 executable programs for several UNIX platforms can be downloaded from the Internet file-transfer protocol (FTP) site <ftp://blast.wustl.edu/blast/executables>. The complete suite of search programs (BLASTP, BLASTN, BLASTX, TBLASTN, and TBLASTX) is provided at that site, in addition to several support programs. WU-BLAST 2.0 is copyrighted and may not be sold or redistributed in any form or manner without the express written consent of the author; but the posted executables may otherwise be freely used for commercial, nonprofit, or academic purposes. In all search programs in the suite -- BLASTP, BLASTN, BLASTX, TBLASTN and TBLASTX -- the gapped alignment routines are integral to the database search itself, and thus yield much better sensitivity and selectivity while producing the more easily interpreted output. Gapping can optionally be turned off in all of these programs, if desired. The default penalty (Q) for a gap of length one is Q=9 for proteins and BLASTP, and Q=10 for BLASTN, but may be changed to any integer value including zero, one through eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. The default per-residue penalty for extending a gap (R) is R=2 for proteins and BLASTP, and R=10 for BLASTN, but may be changed to any integer value including zero, one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve through twenty, twenty-one through fifty, fifty-one through one hundred, etc. Any combination of values for Q and R can be used in order to align sequences so as to maximize overlap and identity

while minimizing sequence gaps. The default amino acid comparison matrix is BLOSUM62, but other amino acid comparison matrices such as PAM can be utilized.

Species homologues of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide. Preferably, polynucleotide species homologues have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, and protein species homologues have at least 30% sequence identity (more preferably, at least 45% identity; most preferably at least 60% identity) with the given protein, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides or the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Species homologues may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species. Preferably, species homologues are those isolated from mammalian species. Most preferably, species homologues are those isolated from certain mammalian species such as, for example, *Pan troglodytes*, *Gorilla gorilla*, *Pongo pygmaeus*, *Hylobates concolor*, *Macaca mulatta*, *Papio papio*, *Papio hamadryas*, *Cercopithecus aethiops*, *Cebus capucinus*, *Aotus trivirgatus*, *Sanguinus oedipus*, *Microcebus murinus*, *Mus musculus*, *Rattus norvegicus*, *Cricetulus griseus*, *Felis catus*, *Mustela vison*, *Canis familiaris*, *Oryctolagus cuniculus*, *Bos taurus*, *Ovis aries*, *Sus scrofa*, and *Equus caballus*, for which genetic maps have been created allowing the identification of syntenic relationships between the genomic organization of genes in one species and the genomic organization of the related genes in another species (O'Brien and Seuánez, 1988, *Ann. Rev. Genet.* 22: 323-351; O'Brien *et al.*, 1993, *Nature Genetics* 3:103-112; Johansson *et al.*, 1995, *Genomics* 25: 682- 690; Lyons *et al.*, 1997, *Nature Genetics* 15: 47-56; O'Brien *et al.*, 1997, *Trends in Genetics* 13(10): 393-399; Carver and Stubbs, 1997, *Genome Research* 7:1123-1137; all of which are incorporated by reference herein).

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotides which also encode proteins which are identical or have significantly similar sequences to those encoded by the disclosed polynucleotides. Preferably, allelic variants have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% identity) with the given polynucleotide, where sequence identity is determined by comparing the nucleotide sequences of the polynucleotides when

aligned so as to maximize overlap and identity while minimizing sequence gaps. Allelic variants may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from individuals of the appropriate species.

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides that hybridize under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M- R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp) [‡]	Hybridization Temperature and Buffer [†]	Wash Temperature and Buffer [†]
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T _B *; 1xSSC	T _B *; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T _D *; 1xSSC	T _D *; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T _F *; 1xSSC	T _F *; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T _H *; 4xSSC	T _H *; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T _J *; 4xSSC	T _J *; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T _L *; 2xSSC	T _L *; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T _N *; 6xSSC	T _N *; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T _P *; 6xSSC	T _P *; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T _R *; 4xSSC	T _R *; 4xSSC

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

†: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH₂PO₄, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6(log₁₀[Na⁺]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na⁺] is the concentration of sodium ions in the hybridization buffer ([Na⁺] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25% (more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may contain sequences at its 5' and/or 3' end that are derived from linker, polylinker, or multiple cloning site sequences commonly found in vectors such as the pMT2 or pED expression vectors (see below). For example, sequences such as SEQ ID NO:626, SEQ ID NO:627, or SEQ ID NO:628 may be found at the 5' end of an isolated polynucleotide of the invention, or the complement of any of these sequences may be found at its 3' end. Similarly, sequences such as SEQ ID NO:629, SEQ ID NO:630, or SEQ ID NO:631 may be found at the 3' end of an isolated polynucleotide of the invention, or the complement of any of these sequences may be found at its 5' end. In addition, variants of these linker sequences may be present in isolated polynucleotides of the invention, which linker variants vary from SEQ ID NO:626 through SEQ ID NO:631 by the alteration, insertion, or deletion of

one or more nucleotides. Therefore, a preferred embodiment of the invention comprises the nucleotide sequence of any of the isolated polynucleotides disclosed herein, beginning at nucleotide 25 and ending at nucleotide (N-25) of the SEQ ID NO for that polynucleotide, where N represents the total number of nucleotides in the sequence. As a specific example, a preferred embodiment of the invention comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 25 to nucleotide 1905, where the total number of nucleotides (N) in SEQ ID NO:1 is 1930, and N-25 equals 1905. More preferably, a polynucleotide of the invention comprises the nucleotide sequence of any of the isolated polynucleotides disclosed herein, beginning at nucleotide 30 and ending at nucleotide (N-30) of the SEQ ID NO for that polynucleotide. Most preferably, a polynucleotide of the invention comprises the nucleotide sequence of any of the isolated polynucleotides disclosed herein, beginning at nucleotide 35 and ending at nucleotide (N-35) of the SEQ ID NO for that polynucleotide. Similarly, additional embodiments are those nucleotide sequences that extend from nucleotide 40 to nucleotide (N-40), or from nucleotide 45 to nucleotide (N-45), or from nucleotide 50 to nucleotide (N-50), or from nucleotide 60 to nucleotide (N-60), or from nucleotide 65 to nucleotide (N-65), or from nucleotide 70 to nucleotide (N-70), or from nucleotide 75 to nucleotide (N-75), or from nucleotide 80 to nucleotide (N-80), etc., for any of the polynucleotides disclosed herein. Further preferred embodiments are those nucleotide sequences that are subsequences of the nucleotide sequences disclosed herein, beginning at any nucleotide position selected from the group consisting of nucleotide 5, nucleotide 10, nucleotide 15, nucleotide 20, nucleotide 25, nucleotide 30, nucleotide 35, nucleotide 40, nucleotide 45, nucleotide 50, nucleotide 55, nucleotide 60, nucleotide 65, nucleotide 70, nucleotide 75, or nucleotide 80, and ending at any nucleotide position selected from the group consisting of nucleotide (N-5), nucleotide (N-10), nucleotide (N-15), nucleotide (N-20), nucleotide (N-25), nucleotide (N-30), nucleotide (N-35), nucleotide (N-40), nucleotide (N-45), nucleotide (N-50), nucleotide (N-55), nucleotide (N-60), nucleotide (N-65), nucleotide (N-70), nucleotide (N-75), or nucleotide (N-80), wherein N is the total number of nucleotides disclosed for a particular SEQ ID NO.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, *Nucleic Acids Res.* 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, *Methods in Enzymology* 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the

protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli*, *Bacillus subtilis*, *Salmonella typhimurium*, or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, e.g., Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin- toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLabs (Beverly, MA), Pharmacia (Piscataway, NJ) and Invitrogen Corporation (Carlsbad, CA), respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from the Eastman Kodak Company (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or

deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The primary use of polynucleotides of the invention which are sESTs is as probes for the identification and isolation of full-length cDNAs and genomic DNA molecules which correspond (i.e., is a longer polynucleotide sequence of which substantially the entire sEST is a fragment in the case of a full-length cDNA, or which encodes the sEST in the case of a genomic DNA molecule) to such sESTs. Techniques for use of such sequences as probes for larger cDNAs or genomic molecules are well known in the art.

The polynucleotides can also be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of

expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions,

suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, *In Vitro* assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, *Immunologic studies in Humans*); Takai et al., *J. Immunol.* 137:3494-3500, 1986; Bertagnolli et al., *J. Immunol.* 145:1706-1712, 1990; Bertagnolli et al., *Cellular Immunology* 133:327-341, 1991; Bertagnolli, et al., *J. Immunol.* 149:3778-3783, 1992; Bowman et al., *J. Immunol.* 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ , Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., *J. Exp. Med.* 173:1205-1211, 1991; Moreau

et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: *Current Protocols in Immunology*, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases caused by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, i.e., in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitus, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as, for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this manner prevents cytokine synthesis by immune

cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, 89:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythematosus in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example,

enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide

having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowman et al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol.

137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad. Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use

in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. *Cellular Biology* 15:141-151, 1995; Keller et al., *Molecular and Cellular Biology* 13:473-486, 1993; McClanahan et al., *Blood* 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., *Proc. Natl. Acad. Sci. USA* 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., *Experimental Hematology* 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 1-21, Wiley-Liss, Inc., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, et al. eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as

well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. *De novo* tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel

syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin- β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779- 782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction

of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenberg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis,

cytokine or chemokine- induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or circadian cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine

composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes

on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunoglobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with

cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of

the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 μ g to about 100 mg (preferably about 0.1mg to about 10 mg, more preferably about 0.1 μ g to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, *J. Amer.Chem.Soc.* 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, *FEBS Lett.* 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably

be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent

useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorption of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF- α and TGF- β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

What is claimed is:

1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134, SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ

ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID NO:241, SEQ ID NO:242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO:245, SEQ ID NO:246, SEQ ID NO:247, SEQ ID NO:248, SEQ ID NO:249, SEQ ID NO:250, SEQ ID NO:251, SEQ ID NO:252, SEQ ID NO:253, SEQ ID NO:254, SEQ ID NO:255, SEQ ID NO:256, SEQ ID NO:257, SEQ ID NO:258, SEQ ID NO:259, SEQ ID NO:260, SEQ ID NO:261, SEQ ID NO:262, SEQ ID NO:263, SEQ ID NO:264, SEQ ID NO:265, SEQ ID NO:266, SEQ ID NO:267, SEQ ID NO:268, SEQ ID NO:269, SEQ ID NO:270, SEQ ID NO:271, SEQ ID NO:272, SEQ ID NO:273, SEQ ID NO:274, SEQ ID NO:275, SEQ ID NO:276, SEQ ID NO:277, SEQ ID NO:278, SEQ ID NO:279, SEQ ID NO:280, SEQ ID NO:281, SEQ ID NO:282, SEQ ID NO:283, SEQ ID NO:284, SEQ ID NO:285, SEQ ID NO:286, SEQ ID NO:287, SEQ ID NO:288, SEQ ID NO:289, SEQ ID NO:290, SEQ ID NO:291, SEQ ID NO:292, SEQ ID NO:293, SEQ ID NO:294, SEQ ID NO:295, SEQ ID NO:296, SEQ ID NO:297, SEQ ID NO:298, SEQ ID NO:299, SEQ ID NO:300, SEQ ID NO:301, SEQ ID NO:302, SEQ ID NO:303, SEQ ID NO:304, SEQ ID NO:305, SEQ ID NO:306, SEQ ID NO:307, SEQ ID NO:308, SEQ ID NO:309, SEQ ID NO:310, SEQ ID NO:311, SEQ ID NO:312, SEQ ID NO:313, SEQ ID NO:314, SEQ ID NO:315, SEQ ID NO:316, SEQ ID NO:317, SEQ ID NO:318, SEQ ID NO:319, SEQ ID NO:320, SEQ ID NO:321, SEQ ID NO:322, SEQ ID NO:323, SEQ ID NO:324, SEQ ID NO:325, SEQ ID NO:326, SEQ ID NO:327, SEQ ID NO:328, SEQ ID NO:329, SEQ ID NO:330, SEQ ID NO:331, SEQ ID NO:332, SEQ ID NO:333, SEQ ID NO:334,

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NO:507, SEQ ID NO:508, SEQ ID NO:509, SEQ ID NO:510, SEQ ID NO:511, SEQ ID NO:512, SEQ ID NO:513, SEQ ID NO:514, SEQ ID NO:515, SEQ ID NO:516, SEQ ID NO:517, SEQ ID NO:518, SEQ ID NO:519, SEQ ID NO:520, SEQ ID NO:521, SEQ ID NO:522, SEQ ID NO:523, SEQ ID NO:524, SEQ ID NO:525, SEQ ID NO:526, SEQ ID NO:527, SEQ ID NO:528, SEQ ID NO:529, SEQ ID NO:530, SEQ ID NO:531, SEQ ID NO:532, SEQ ID NO:533, SEQ ID NO:534, SEQ ID NO:535, SEQ ID NO:536, SEQ ID NO:537, SEQ ID NO:538, SEQ ID NO:539, SEQ ID NO:540, SEQ ID NO:541, SEQ ID NO:542, SEQ ID NO:543, SEQ ID NO:544, SEQ ID NO:545, SEQ ID NO:546, SEQ ID NO:547, SEQ ID NO:548, SEQ ID NO:549, SEQ ID NO:550, SEQ ID NO:551, SEQ ID NO:552, SEQ ID NO:553, SEQ ID NO:554, SEQ ID NO:555, SEQ ID NO:556, SEQ ID NO:557, SEQ ID NO:558, SEQ ID NO:559, SEQ ID NO:560, SEQ ID NO:561, SEQ ID NO:562, SEQ ID NO:563, SEQ ID NO:564, SEQ ID NO:565, SEQ ID NO:566, SEQ ID NO:567, SEQ ID NO:568, SEQ ID NO:569, SEQ ID NO:570, SEQ ID NO:571, SEQ ID NO:572, SEQ ID NO:573, SEQ ID NO:574, SEQ ID NO:575, SEQ ID NO:576, SEQ ID NO:577, SEQ ID NO:578, SEQ ID NO:579, SEQ ID NO:580, SEQ ID NO:581, SEQ ID NO:582, SEQ ID NO:583, SEQ ID NO:584, SEQ ID NO:585, SEQ ID NO:586, SEQ ID NO:587, SEQ ID NO:588, SEQ ID NO:589, SEQ ID NO:590, SEQ ID NO:591, SEQ ID NO:592, SEQ ID NO:593, SEQ ID NO:594, SEQ ID NO:595, SEQ ID NO:596, SEQ ID NO:597, SEQ ID NO:598, SEQ ID NO:599, SEQ ID NO:600, SEQ ID NO:601, SEQ ID NO:602, SEQ ID NO:603, SEQ ID NO:604, SEQ ID NO:605, SEQ ID NO:606, SEQ ID NO:607, SEQ ID NO:608, SEQ ID NO:609, SEQ ID NO:610, SEQ ID NO:611, SEQ ID NO:612, SEQ ID NO:613, SEQ ID NO:614, SEQ ID NO:615, SEQ ID NO:616, SEQ ID NO:617, SEQ ID NO:618, SEQ ID NO:619, SEQ ID NO:620, SEQ ID NO:621, SEQ ID NO:622, SEQ ID NO:623, SEQ ID NO:624, SEQ ID NO:625;

or a complement of said sequence.

2. An isolated polynucleotide consisting of a nucleotide sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID

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or a complement of said sequence.

3. An isolated polynucleotide comprising a nucleotide sequence which hybridizes to a sequence selected from the group consisting of:

SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID

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or to a complement of said sequence.

4. The polynucleotide of any one of claims 1-3, wherein said polynucleotide is operably linked to at least one expression control sequence.

5. A vector comprising the polynucleotide of claim 4.

6. A host cell transformed with a vector comprising the polynucleotide of any one of claims 1-3.

7. A process for producing a protein encoded by the polynucleotide of claim 4, which process comprises:

- (a) growing a culture of a host cell in a suitable culture medium, wherein the host cell has been transformed with the polynucleotide of claim 4; and
- (b) purifying said protein from the culture.

8. A protein produced according to the process of claim 7.

9. An antibody that specifically binds to the protein of claim 8.

10. A method for detecting the protein of claim 8, comprising contacting a sample suspected of containing the protein with an antibody that specifically binds to the protein, under conditions such that the antibody binds the protein and the protein is detected.

11. A method for detecting the polynucleotide of any one of claims 1-3, comprising contacting a sample suspected of containing the polynucleotide with a polynucleotide reagent that hybridizes to the polynucleotide, under conditions such that the reagent binds the polynucleotide and the polynucleotide is detected.

12. The method of claim 10, wherein the sample is a biological sample.

13. The method of claim 12, where the biological sample is isolated from a human.
14. The method of claim 11, wherein the sample is a biological sample.
15. The method of claim 14, where the biological sample is isolated from a human.
16. A method of identifying a compound that modulates the activity of the protein of claim 8, comprising contacting a composition comprising the protein with a test compound and monitoring the effect of the test compound on the activity of the protein, such that a modulatory compound is identified.
17. A method of identifying a compound that modulates the expression of the polynucleotide of any one of claims 1-3, comprising contacting a cell that expresses the polynucleotide with a test compound and determining the effect of the test compound on the expression of the polynucleotide, such that a modulatory compound is identified.
18. A method of identifying a compound that modulates the production of the protein of claim 8, comprising contacting a cell that produces the protein with the test compound and determining the effect of the test compound on the production of the protein, such that a modulatory compound is identified.
19. A method of treating a subject having a disorder characterized by aberrant expression of the polynucleotide of any one of claims 1-3, comprising administering to said subject a therapeutically effective amount of a compound that modulates expression of the polypeptide, such that treatment is effected.
20. A method of treating a subject having a disorder characterized by aberrant production of the protein of claim 8, comprising administering to said subject a therapeutically effective amount of a compound that modulates production of the protein, such that treatment is effected.
21. A method of treating a subject having a disorder characterized by aberrant activity of the protein of claim 8, comprising administering to said subject a therapeutically effective amount of a compound that modulates activity of the protein, such that treatment is effected.

SEQUENCE LISTING

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 Clark, Hilary
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 Agostino, Michael J.
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<212> DNA

<213> Homo sapiens

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<211> 2144

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 1745

<212> DNA

<213> Homo sapiens

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<211> 2157

<212> DNA

<213> Homo sapiens

<400> 11

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 2740

<212> DNA

<213> Homo sapiens

<400> 36

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<210> 37

<211> 1928

<212> DNA

<213> Homo sapiens

<400> 37

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<212> DNA

<213> Homo sapiens

<400> 38

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<210> 39

<211> 2732

<212> DNA

<213> Homo sapiens

<400> 39

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<211> 2201

<212> DNA

<213> Homo sapiens

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<211> 1727

<212> DNA

<213> Homo sapiens

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<211> 1749

<212> DNA

<213> Homo sapiens

<400> 42

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<210> 43

<211> 1740

<212> DNA

<213> Homo sapiens

<400> 43

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<211> 2454

<212> DNA

<213> Homo sapiens

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<211> 2270

<212> DNA

<213> Homo sapiens

<400> 45

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<211> 1482

<212> DNA

<213> Homo sapiens

<400> 46

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<211> 2588

<212> DNA

<213> Homo sapiens

<400> 47

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 <211> 2222
 <212> DNA
 <213> Homo sapiens

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<210> 49
 <211> 2176
 <212> DNA
 <213> Homo sapiens

<400> 49

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<211> 2101

<212> DNA

<213> Homo sapiens

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<210> 51
 <211> 1439
 <212> DNA
 <213> Homo sapiens

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 <211> 1842
 <212> DNA
 <213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 1545

<212> DNA

<213> Homo sapiens

<400> 54

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<211> 1352

<212> DNA

<213> Homo sapiens

<400> 55

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<211> 2756

<212> DNA

<213> Homo sapiens

<400> 56

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<210> 57

<211> 1499

<212> DNA

<213> Homo sapiens

<400> 57

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<210> 58

<211> 1463

<212> DNA

<213> Homo sapiens

<400> 58

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<210> 59

<211> 614

<212> DNA

<213> Homo sapiens

<400> 59

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<211> 2160

<212> DNA

<213> Homo sapiens

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<210> 61

<211> 1788

<212> DNA

<213> Homo sapiens

<400> 61

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<210> 62

<211> 1753

<212> DNA

<213> Homo sapiens

<400> 62

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<210> 63

<211> 1244

<212> DNA

<213> Homo sapiens

<400> 63

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<210> 64

<211> 1725

<212> DNA

<213> Homo sapiens

<400> 64

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<210> 65

<211> 1098

<212> DNA

<213> Homo sapiens

<400> 65

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<210> 66

<211> 2407

<212> DNA

<213> Homo sapiens

<400> 66

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<210> 67

<211> 1575

<212> DNA

<213> Homo sapiens

<400> 67

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<210> 68

<211> 1553

<212> DNA

<213> Homo sapiens

<400> 68

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<210> 69

<211> 2680

<212> DNA

<213> Homo sapiens

<400> 69

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<210> 70

<211> 2266

<212> DNA

<213> Homo sapiens

<400> 70

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<210> 71

<211> 2102

<212> DNA

<213> Homo sapiens

<400> 71

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<210> 72
 <211> 731
 <212> DNA
 <213> Homo sapiens

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<210> 73
 <211> 1165
 <212> DNA
 <213> Homo sapiens

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<210> 74
 <211> 1808
 <212> DNA
 <213> Homo sapiens

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<400> 74
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<210> 75

<211> 2670

<212> DNA

<213> Homo sapiens

<400> 75

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<211> 1976

<212> DNA

<213> Homo sapiens

<400> 76

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<211> 1746

<212> DNA

<213> Homo sapiens

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<210> 84

<211> 1167

<212> DNA

<213> Homo sapiens

<400> 84

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<210> 85

<211> 1641

<212> DNA

<213> Homo sapiens

<400> 85

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<210> 86

<211> 1892

<212> DNA

<213> Homo sapiens

<400> 86

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<210> 87

<211> 1668

<212> DNA

<213> Homo sapiens

<400> 87

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<210> 88

<211> 1849

<212> DNA

<213> Homo sapiens

<400> 88

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<211> 1508

<212> DNA

<213> Homo sapiens

<400> 89

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<211> 1532

<212> DNA

<213> Homo sapiens

<400> 90

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<211> 1951

<212> DNA

<213> Homo sapiens

<400> 91

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 <213> Homo sapiens

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<211> 1527

<212> DNA

<213> Homo sapiens

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<210> 96

<211> 1954

<212> DNA

<213> Homo sapiens

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<211> 2378

<212> DNA

<213> Homo sapiens

<400> 97

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<211> 3335

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 2561

<212> DNA

<213> Homo sapiens

<400> 100

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<211> 2041

<212> DNA

<213> Homo sapiens

<400> 101

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<212> DNA

<213> Homo sapiens

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<211> 1969

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<210> 106

<211> 1786

<212> DNA

<213> Homo sapiens

<400> 106

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<211> 3172

<212> DNA

<213> Homo sapiens

<400> 107

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<211> 2538

<212> DNA

<213> Homo sapiens

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<211> 1606

<212> DNA

<213> Homo sapiens

<400> 109

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<212> DNA

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<211> 1679

<212> DNA

<213> Homo sapiens

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<211> 2444

<212> DNA

<213> Homo sapiens

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<211> 1389

<212> DNA

<213> Homo sapiens

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<211> 2456

<212> DNA

<213> Homo sapiens

<400> 114

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<212> DNA

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<211> 1673

<212> DNA

<213> Homo sapiens

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<210> 117

<211> 1368

<212> DNA

<213> Homo sapiens

<400> 117

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<210> 118

<211> 1493

<212> DNA

<213> Homo sapiens

<400> 118

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<210> 119

<211> 1753

<212> DNA

<213> Homo sapiens

<400> 119

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<210> 120

<211> 1340

<212> DNA

<213> Homo sapiens

<400> 120

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<210> 121

<211> 2077

<212> DNA

<213> Homo sapiens

<400> 121

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<210> 122

<211> 1830

<212> DNA

<213> Homo sapiens

<400> 122

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<210> 123

<211> 1962

<212> DNA

<213> Homo sapiens

<400> 123

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<210> 124
 <211> 1506
 <212> DNA
 <213> Homo sapiens

<400> 124
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 <213> Homo sapiens

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<210> 126

<211> 1561

<212> DNA

<213> Homo sapiens

<400> 126

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<210> 127

<211> 1651

<212> DNA

<213> Homo sapiens

<400> 127

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<210> 128

<211> 1801

<212> DNA

<213> Homo sapiens

<400> 128

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<210> 129

<211> 1510

<212> DNA

<213> Homo sapiens

<400> 129

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<210> 130

<211> 1496

<212> DNA

<213> Homo sapiens

<400> 130

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<210> 131

<211> 753

<212> DNA

<213> Homo sapiens

<400> 131

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<210> 132

<211> 565

<212> DNA

<213> Homo sapiens

<400> 132

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<210> 133

<211> 1761

<212> DNA

<213> Homo sapiens

<400> 133

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<210> 134
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 <212> DNA
 <213> Homo sapiens

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<210> 135
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 <212> DNA
 <213> Homo sapiens

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<210> 136

<211> 1854

<212> DNA

<213> Homo sapiens

<400> 136

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<210> 137

<211> 1501

<212> DNA

<213> Homo sapiens

<400> 137

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<211> 1613

<212> DNA

<213> Homo sapiens

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<211> 780

<212> DNA

<213> Homo sapiens

<400> 139

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<212> DNA
<213> Homo sapiens

<400> 140
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<211> 2198
<212> DNA
<213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

<400> 142
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 <211> 2229
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 <213> Homo sapiens

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<210> 144

<211> 794

<212> DNA

<213> Homo sapiens

<400> 144

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<210> 145

<211> 1216

<212> DNA

<213> Homo sapiens

<400> 145

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acccagaacc caagatacct catcacagt actggaaaga agttaacagt gacttgttct 180
cagaatatga accatgagta tatgtcctgg tatcgacaag acccagggtt gggcttaagg 240
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<210> 146

<211> 962

<212> DNA

<213> Homo sapiens

<400> 146

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<210> 147

<211> 1229

<212> DNA

<213> Homo sapiens

<400> 147

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<210> 148
 <211> 1389
 <212> DNA
 <213> Homo sapiens

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<400> 148
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<210> 149
 <211> 676
 <212> DNA
 <213> Homo sapiens

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<400> 149
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<210> 150
 <211> 1163
 <212> DNA
 <213> Homo sapiens

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<210> 151

<211> 1044

<212> DNA

<213> Homo sapiens

<400> 151

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<210> 152

<211> 1072

<212> DNA

<213> Homo sapiens

<400> 152

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ttagcataaa tgttgtgcat tttatcttag tgtttggatg aaaacatttg tgttgttttag 960
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<210> 153

<211> 1121

<212> DNA

<213> Homo sapiens

<400> 153

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 tccatgagct gacggtgcac gaggtcgct gcgcccaccc gaccaagaca ggagtgagc 180
 tgatggagat cctggatggg atggaccaga gccaccgcaa ggagatgcag ctgtacaaca 240
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 cgtggagtgc aacaagctgc tggctgcca gaacatcaac ctgcggctct tccgtttcca 660
 gatacagaag tagggcgggg cctcaggatg tccgaggagc ccacggggcg catcccagca 720
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<210> 154

<211> 722

<212> DNA

<213> Homo sapiens

<400> 154

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 gggcctgggc cctttcccaa cccctcctag gatgtgcggg cagtgtgctg gcgcctcaca 180
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 ggggaagggtg ggtggcttta gaattaaggc ccttgtaggc tttggcaggt aagagggccc 600
 aaggttaagaa cgagagccaa cgggcacaag cattctatat ataagtggct cattaggtgt 660
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<210> 155

<211> 373

<212> DNA

<213> Homo sapiens

<400> 155

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 gaactaccaa cttgtttcta aagagctatc ttaagaccaa tatctctttg tttttaaaca 180
 aaagatatta ttttgtgtat gaatctaaat caagcccatc tgtcattatg ttactgtctt 240
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 gtgaatgtaa gctcttaact atgtctcttt gtaatgtgta atttctttct gaaataaaac 360
 catttgtgaa tat 373

<210> 156
 <211> 1027
 <212> DNA
 <213> Homo sapiens

<400> 156
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 gatgcaaaag tgaagctgtg gtctaccaat ctagacaact cagtggcaag cattgaggca 180
 aaggctaatt tgtgctgtgt taaattcagc ccctcttcca gataccattt ggctttcggc 240
 tgtgcagatc actgtgtcca ctactatgat ctctgtaaca ctaaacagcc aatcatggta 300
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 cccagccaac tctccaccat caatgtaact ccatggacat tgctgctctt ggtggtgtta 960
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<210> 157
 <211> 790
 <212> DNA
 <213> Homo sapiens

<400> 157
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 gcaatttaag attttagtg actacatctg tgaaggggccc tttgaatttg aggtctatgg 180
 gcgggtcgag gaccaggatc tgctcgtgct tcgcctgtgc cccggaggca gacgccattg 240
 gagagacagc gcagagcagg gggcggtctg ctgcgtgggg gcgggggacg atggcgagag 300
 gggaggggga gcgagttcgc atctctcctt ttcttggtta gactctgttc aaccacattc 360
 ttatgttggc agatctgctt ccagattgat ttttagagca ccatcacttt cacattcctg 420
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 tatgttctca tattactttt gattctacta tgattgtgtg gtggtgaaca aagatcatta 720
 caaacaaaaa ctgtaatttt gttatatttg attcaatgga atttacctaa aaaataaaga 780
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<210> 158
 <211> 526
 <212> DNA
 <213> Homo sapiens

<400> 158
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 aaacgagggc tacaacaata ttgttttaca aatactagca cttttttttc tgttatgtac 120
 ttagtgtagg aggggtcaaaa taatctttct gcttagcatc tcttaaacca tacctgcaaa 180
 tatagcagga ttattacatt tacagtactt taatacttgt ataaactatg cagaaatttt 240
 taataaagtg taatatattt tataagctaa taagactgaa tgggtaaagg ttttttagcat 300
 gcgttagtat acttgcagat actgaaacat tttggtaac tttcttacta aagatgtgaa 360
 tgttttaagt accttctctg tttctactct gtagtccaat gggaattcag taatgacatt 420
 ttgtcatgtc aaactgtgaa cataaatttg tactgtacag tctcatata ctatatacag 480
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<210> 159
 <211> 778

<212> DNA

<213> Homo sapiens

<400> 159

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agctgcacat  gttagccaca  gagccacccc  caggcatcac  atgttggcaa  gataaagacc  180
aaatggatga  cctgcgagct  caaatattag  gtggagccaa  cacaccttat  gagaaaggtg  240
tttttaagct  agaagttatc  attcctgaga  ggtacccatt  tgaacctcct  cagatccgat  300
ttctcagtc  aatttatcat  ccaaacattg  attctgctgg  aaggatttgt  ctggatgttc  360
tcaaattgcc  accaaaaggt  gcttggagac  catccctcaa  catcgcaact  gtgttgacct  420
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cggaatttaa  atataataag  cgggccttct  tcaagaatgc  cagacagtgg  acagagaagc  540
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aaaagaaatt  tcatcctgat  gtttagggga  cttgtcctgg  ttcatcttag  ttaatgtgtt  720
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<210> 160

<211> 1147

<212> DNA

<213> Homo sapiens

<400> 160

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attatggaga  atttaaat  ttataaaatg  ttttctctcc  cctaaagaag  atttttgttt  180
gagccaagac  aaaaacatga  aaatttaatg  cagacctct  ataaaaagta  ttattgtatg  240
tcatctttaa  cttattaaat  gaaagcttct  aaacagtgg  aaagaagagg  gtagcaaatg  300
cccaccttta  aattatcaac  attttccaaa  tcatttttaa  accaacttgt  aaatgtcatt  360
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gatttgtag  tagtgaagat  actatgggtg  agatgaagga  agaaagagta  gtgttcttaa  540
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gcctgtagtc  ccagctactc  gggaggctga  ggcaggagaa  tgggtgtgagc  ctgggaggca  1080
gagcttgacg  tgagccaaca  tcgcaccact  gcactccagc  ctgggcaaca  aagcgagact  1140
ccatctc                                           1147

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<210> 161

<211> 636

<212> DNA

<213> Homo sapiens

<400> 161

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cagatogaag  tatttcacaa  gaatacttgt  gtttttaaca  gcccttcccc  tggacggtgc  60
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cggtttttaa  gggagcagga  aaaatgcgtc  tgagagcaac  tctttttaa  aacctgccct  180
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aaacgtttaa  aggggccaag  atttgccga  gggttactcc  tttgctctca  ccttgtagtg  300
atgaggagat  gaagccattt  cttatcctgt  agatgtgaag  cactttcagt  tttcagcgat  360
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taatttaaat  gtcacagaca  atgtcctagt  gttgactact  acaatgttga  tgctacactg  600
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<210> 162

<211> 1224
 <212> DNA
 <213> Homo sapiens

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 ggctaggata tctgctctga agaacctcat tcagttctct cttatccagg ttatccagg 420
 gaatttttgg ccaatatattg tctagcaaag tagcatgact gttagcggt cgataccaat 480
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 gacagtcacc tcggccagga atcaagagct ctccattctc caagagagg atcagcacag 600
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 aagaactcct attaccacc agctctccag gggctggcag ctgccaggc agcaccacag 1020
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<210> 163
 <211> 1015
 <212> DNA
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 aaatacagaa ggaaacttgt gtctcaagaa gaaatggaat ttatccaacg tggaggtcct 180
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 aatgaaatat agaaaattta gatggacact tgtatttctt aatttatgta tcttggtcag 360
 cttctccaca agcttaccta attgtttata tactttatac ttattaaagt atacattttt 420
 aaatgttagc ctattaattt actcttgatt atcaaacatt accagtgttg aactattaaa 480
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<210> 164
 <211> 1167
 <212> DNA
 <213> Homo sapiens

<400> 164
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cagtgactg gagaggggag agcatggatc ctgggggtcaa agggcctttg cccccaccct 540
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<210> 165

<211> 1253

<212> DNA

<213> Homo sapiens

<400> 165

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<210> 166

<211> 1328

<212> DNA

<213> Homo sapiens

<400> 166

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1328

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<211> 451

<212> DNA

<213> Homo sapiens

<400> 167

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<210> 168

<211> 913

<212> DNA

<213> Homo sapiens

<400> 168

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<210> 169

<211> 1072

<212> DNA

<213> Homo sapiens

<400> 169

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<210> 170

<211> 1114

<212> DNA

<213> Homo sapiens

<400> 170

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<210> 171

<211> 1111

<212> DNA

<213> Homo sapiens

<400> 171

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<210> 172

<211> 858

<212> DNA

<213> Homo sapiens

<400> 172

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<210> 173

<211> 18

<212> DNA

<213> Homo sapiens

<400> 173

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18

<210> 174

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<212> DNA

<213> Homo sapiens

<400> 174

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<211> 496

<212> DNA

<213> Homo sapiens

<400> 175

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 <212> DNA
 <213> Homo sapiens

<400> 177
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<210> 178
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 <212> DNA
 <213> Homo sapiens

<400> 178

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<211> 2996

<212> DNA

<213> Homo sapiens

<400> 179

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<211> 1317

<212> DNA

<213> Homo sapiens

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<210> 181

<211> 791

<212> DNA

<213> Homo sapiens

<400> 181

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<210> 182

<211> 1226

<212> DNA

<213> Homo sapiens

<400> 182

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<211> 1342

<212> DNA

<213> Homo sapiens

<400> 183

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<211> 2633

<212> DNA

<213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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<210> 188
<211> 1666
<212> DNA
<213> Homo sapiens

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<400> 188
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<210> 189
<211> 1242
<212> DNA
<213> Homo sapiens

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<400> 189
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<210> 190

<211> 1956

<212> DNA

<213> Homo sapiens

<400> 190

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<210> 191

<211> 1799

<212> DNA

<213> Homo sapiens

<400> 191

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<210> 192

<211> 1298

<212> DNA

<213> Homo sapiens

<400> 192

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ctagaaaatt tggaaaatac aaaatcccat aaaaaataaa aatcacacat aatccgccca 540
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<210> 193

<211> 1342

<212> DNA

<213> Homo sapiens

<400> 193

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tatttgctta aacatcctgt ttaacaactt tataacatcc ttcggaattt ttaaggtaat 180
aatgtgagat ataagtatga taaaaaacac ttttaaatgg tatttaatgc aaatacagaa 240
taacgatgtc aacattttcc tcagccgtgt aacctgagat tcatcatggg aatgagaaag 300
taaaggccct ttgtaatggc atgtgaacca gacaatttag tagccagggt tgtaaggcaa 360

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<210> 194

<211> 1116

<212> DNA

<213> Homo sapiens

<400> 194

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<210> 195

<211> 2831

<212> DNA

<213> Homo sapiens

<400> 195

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<210> 196

<211> 988

<212> DNA

<213> Homo sapiens

<400> 196

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<211> 1015

<212> DNA

<213> Homo sapiens

<400> 197

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<210> 198

<211> 894

<212> DNA

<213> Homo sapiens

<400> 198

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gactgttggt ggggtggggg gagaggggag ggataacatc gggagatata cctaagtcta 780
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<210> 199

<211> 1192

<212> DNA

<213> Homo sapiens

<400> 199

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<210> 200

<211> 899

<212> DNA

<213> Homo sapiens

<400> 200

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<210> 201

<211> 3260

<212> DNA

<213> Homo sapiens

<400> 201

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<210> 202

<211> 1495

<212> DNA

<213> Homo sapiens

<400> 202

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<210> 203

<211> 2416

<212> DNA

<213> Homo sapiens

<400> 203

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<210> 205
<211> 1026
<212> DNA
<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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 <213> Homo sapiens

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<211> 1334

<212> DNA

<213> Homo sapiens

<400> 216

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 <212> DNA
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 <212> DNA
 <213> Homo sapiens

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<211> 766

<212> DNA

<213> Homo sapiens

<400> 222

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ccgctgaccc tgagtgaagg ccgcctgccg gggactcaga cactcagggg acaaaatggg 660
cagccagagc tggggaaacc cagaactgac ttcaaaggca gcttctggac aggtggtggg 720
aggggaccc tcccaagagg aaccaataaa ccttctgtgc agaattg 766

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<210> 223
 <211> 1586
 <212> DNA
 <213> Homo sapiens

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<400> 223
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<210> 224
 <211> 1045
 <212> DNA
 <213> Homo sapiens

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<400> 224
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tctttagagg aaaaggaaat ggagaatttt gtcagtgtta catgggctca cagaaacaat 300
ttaaaattac taaactttca ccagcaatgg gctgtaaatt cagactatcg gccagaaatg 360
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<210> 225

<211> 2153

<212> DNA

<213> Homo sapiens

<400> 225

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caaccacgtt cctgtcatca ccacactgct acgaggaggg gcccggtgag atgccctgga 780
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aattctggct gantttagaa ctctaaggga ataaatttgt gttgttttaa gtc 2153

```

<210> 226

<211> 1704

<212> DNA

<213> Homo sapiens

<400> 226

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ttcaaactaa tgttgttcaa gagtcaactg tataaaagg ataatatgt ctggaaagag 180
atatgtttcc aatttaacag acactacca tgaggagaag agttgggcta ggcaggaaac 240
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caggtttatt agaagaaaat gcagattcct gaaacttctc gcagacccca tgagtgaaca 360
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gtgtatatct gagtttcagt agcactgcta atcaattggt tgggggtctc tctctcac 480
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```

```

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gtggacgcca tgtgatctta gaaa 1704

```

<210> 227

<211> 2267

<212> DNA

<213> Homo sapiens

<400> 227

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gcacatggat tcacataaac tgaatgggtg aatgtctggg caaccaaacc tgttggcttt 180
tgagaaaact gtcaaatact ttaacatcaa actgttgcaa tgcaagggtat ttcttttgatt 240
gtttcttcaca aaatatggtt aaaccaagta tatacatgt agctagcttc agtaaattgt 300
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aagtcattaa atttttttgc agaactgaaa cttgtatgtt attagtttat tttcttagac 480
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agtcgtttca ggagaatttt tcctatattg ttaccttgat tcattgttta aaattggtag 600
gatttgtata gatataggat agtgttttat ttatacttta tcataagcca taatcatttt 660
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tctccactgt tatccctttg ggggttttta atataaatta ttagtttaca tcatttttgt 2220
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```

<210> 228

<211> 2682

<212> DNA

<213> Homo sapiens

<400> 228

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```

<210> 229

<211> 1612

<212> DNA

<213> Homo sapiens

<400> 229

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cgagatggca ccactgcact ccagcctggg tgagagagta aaaccctttc ac 1612

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<210> 230
 <211> 1512
 <212> DNA
 <213> Homo sapiens

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<400> 230
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 <212> DNA
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<211> 2376

<212> DNA

<213> Homo sapiens

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 <211> 1789
 <212> DNA
 <213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<400> 234

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<210> 235

<211> 1254

<212> DNA

<213> Homo sapiens

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<210> 236

<211> 1117

<212> DNA

<213> Homo sapiens

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<210> 237
 <211> 1572
 <212> DNA
 <213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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<400> 238
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gttacataat acagcttcag tgatttttct tcaaaaatca taaaatcagt gtagagactt 240
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<210> 239

<211> 1952

<212> DNA

<213> Homo sapiens

<400> 239

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<210> 240

<211> 1228

<212> DNA

<213> Homo sapiens

<400> 240

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<210> 241

<211> 1791

<212> DNA

<213> Homo sapiens

<400> 241

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<210> 242

<211> 3196

<212> DNA

<213> Homo sapiens

<400> 242

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<210> 243

<211> 1413

<212> DNA

<213> Homo sapiens

<400> 243

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<210> 244

<211> 1183

<212> DNA

<213> Homo sapiens

<400> 244

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<210> 245

<211> 2017

<212> DNA

<213> Homo sapiens

<400> 245

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<210> 246
 <211> 1441
 <212> DNA
 <213> Homo sapiens

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<400> 246
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<210> 247
 <211> 537
 <212> DNA
 <213> Homo sapiens

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<400> 247
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tcacctggaa caagagctgg aggcagccgc ttgccaggga ggcttgtccc ctgtaagtgc 180

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tttcgggaag agtggcatgt ggcgctgagc cctgtcccgg gcggcacctg ggcgtttcag 240
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<210> 248

<211> 1686

<212> DNA

<213> Homo sapiens

<400> 248

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tgcgcaaac cactttctt aagcacactg gacacccttc gagtgtgggt tttaacatcc 1620
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ttatcc 1686

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<210> 249

<211> 1047

<212> DNA

<213> Homo sapiens

<400> 249

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cggccctcgc tctgcagctg gtgcaaagct ttggctgcca ggctggcca catggcagcc 480
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<210> 250
 <211> 1088
 <212> DNA
 <213> Homo sapiens

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<400> 250
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tcagactgtc  tcatggtggt  gcagttctta  cgaaactttg  gtaaagtttt  gggctttgat  180
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aaaaaaag    1088

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<210> 251
 <211> 1450
 <212> DNA
 <213> Homo sapiens

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<400> 251
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cactaccacc  1450

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<210> 252
 <211> 2477

<212> DNA

<213> Homo sapiens

<400> 252

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<210> 253

<211> 1120

<212> DNA

<213> Homo sapiens

<400> 253

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<210> 254
 <211> 1736
 <212> DNA
 <213> Homo sapiens

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<400> 254
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<210> 255
 <211> 1116
 <212> DNA
 <213> Homo sapiens

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<400> 255
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<210> 256

<211> 2039

<212> DNA

<213> Homo sapiens

<400> 256

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<210> 257

<211> 1338

<212> DNA

<213> Homo sapiens

<400> 257

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<210> 258

<211> 1213

<212> DNA

<213> Homo sapiens

<400> 258

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<210> 259

<211> 957

<212> DNA

<213> Homo sapiens

<400> 259

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<210> 260
 <211> 1085
 <212> DNA
 <213> Homo sapiens

<400> 260
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<210> 261
 <211> 2152
 <212> DNA
 <213> Homo sapiens

<400> 261
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<210> 262

<211> 2074

<212> DNA

<213> Homo sapiens

<400> 262

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<210> 263

<211> 1313

<212> DNA

<213> Homo sapiens

<400> 263

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<210> 264

<211> 2330

<212> DNA

<213> Homo sapiens

<400> 264

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<210> 265

<211> 1046

<212> DNA

<213> Homo sapiens

<400> 265

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1046

<210> 266

<211> 1009

<212> DNA

<213> Homo sapiens

<400> 266

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<210> 267

<211> 2154

<212> DNA

<213> Homo sapiens

<400> 267

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<210> 268

<211> 2248

<212> DNA

<213> Homo sapiens

<400> 268

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 <212> DNA
 <213> Homo sapiens

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 <212> DNA
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<211> 3515

<212> DNA

<213> Homo sapiens

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<211> 2317

<212> DNA

<213> Homo sapiens

<400> 273

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<211> 1267

<212> DNA

<213> Homo sapiens

<400> 274

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<211> 1439

<212> DNA

<213> Homo sapiens

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<210> 276

<211> 2035

<212> DNA

<213> Homo sapiens

<400> 276

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<211> 1370

<212> DNA

<213> Homo sapiens

<400> 277

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<400> 278

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 <212> DNA
 <213> Homo sapiens

<400> 279

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<212> DNA

<213> Homo sapiens

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<211> 2663

<212> DNA

<213> Homo sapiens

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 <213> Homo sapiens

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<211> 1886

<212> DNA

<213> Homo sapiens

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<211> 1439

<212> DNA

<213> Homo sapiens

<400> 284

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<211> 1195

<212> DNA

<213> Homo sapiens

<400> 285

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<213> Homo sapiens

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<211> 931

<212> DNA

<213> Homo sapiens

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<211> 1574

<212> DNA

<213> Homo sapiens

<400> 288

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<211> 1685
 <212> DNA
 <213> Homo sapiens

<400> 289

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1685

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 <211> 1545
 <212> DNA
 <213> Homo sapiens

<400> 290

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 <211> 1936
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 <213> Homo sapiens

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<210> 292
 <211> 1635
 <212> DNA
 <213> Homo sapiens

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<210> 293

<211> 1011

<212> DNA

<213> Homo sapiens

<400> 293

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<210> 294

<211> 1175

<212> DNA

<213> Homo sapiens

<400> 294

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1175

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<211> 1576

<212> DNA

<213> Homo sapiens

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<210> 296

<211> 1151

<212> DNA

<213> Homo sapiens

<400> 296

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 <212> DNA
 <213> Homo sapiens

<400> 298
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 <211> 1037
 <212> DNA

<213> Homo sapiens

<400> 299

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<210> 300

<211> 1424

<212> DNA

<213> Homo sapiens

<400> 300

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<210> 301

<211> 2565

<212> DNA

<213> Homo sapiens

<400> 301

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<210> 302
<211> 1643
<212> DNA
<213> Homo sapiens

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<210> 303
<211> 1634
<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<210> 305

<211> 1501

<212> DNA

<213> Homo sapiens

<400> 305

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<211> 1803

<212> DNA

<213> Homo sapiens

<400> 306

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<211> 1539

<212> DNA

<213> Homo sapiens

<400> 307

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<211> 1793

<212> DNA

<213> Homo sapiens

<400> 308

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<211> 924

<212> DNA

<213> Homo sapiens

<400> 309

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<213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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 <212> DNA
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<210> 317
 <211> 1251
 <212> DNA
 <213> Homo sapiens

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 <211> 787
 <212> DNA
 <213> Homo sapiens

<400> 318

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<210> 319

<211> 1282

<212> DNA

<213> Homo sapiens

<400> 319

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<210> 320

<211> 2497

<212> DNA

<213> Homo sapiens

<400> 320

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 <211> 1645
 <212> DNA
 <213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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<211> 1687

<212> DNA

<213> Homo sapiens

<400> 323

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<211> 2356

<212> DNA

<213> Homo sapiens

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<210> 325
 <211> 1224
 <212> DNA
 <213> Homo sapiens

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 <212> DNA
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1931

<210> 327

<211> 1742

<212> DNA

<213> Homo sapiens

<400> 327

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1742

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 <213> Homo sapiens

<400> 328

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<210> 329
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 <212> DNA
 <213> Homo sapiens

<400> 329

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<211> 1434

<212> DNA

<213> Homo sapiens

<400> 333

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<213> Homo sapiens

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<210> 335

<211> 1963

<212> DNA

<213> Homo sapiens

<400> 335

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<210> 336

<211> 1514

<212> DNA

<213> Homo sapiens

<400> 336

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<210> 337

<211> 1322

<212> DNA

<213> Homo sapiens

<400> 337

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<210> 338

<211> 1857

<212> DNA

<213> Homo sapiens

<400> 338

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<210> 339

<211> 1290

<212> DNA

<213> Homo sapiens

<400> 339

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<210> 340

<211> 1925
 <212> DNA
 <213> Homo sapiens

<400> 340

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<210> 341
 <211> 1106
 <212> DNA
 <213> Homo sapiens
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 <212> DNA
 <213> Homo sapiens

<400> 342
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 <211> 1009
 <212> DNA
 <213> Homo sapiens

<400> 343
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<210> 344
 <211> 1445

<212> DNA
<213> Homo sapiens

<400> 344

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<210> 345
<211> 1682
<212> DNA
<213> Homo sapiens

<400> 345

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cc

1682

<210> 346
 <211> 1164
 <212> DNA
 <213> Homo sapiens

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<210> 347
 <211> 2160
 <212> DNA
 <213> Homo sapiens

<400> 347
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<210> 348

<211> 1663

<212> DNA

<213> Homo sapiens

<400> 348

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<210> 349

<211> 2190

<212> DNA

<213> Homo sapiens

<400> 349

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<210> 350

<211> 1013

<212> DNA

<213> Homo sapiens

<400> 350

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<210> 351

<211> 1023

<212> DNA

<213> Homo sapiens

<400> 351

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<210> 352
 <211> 1279
 <212> DNA
 <213> Homo sapiens

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<400> 352
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<210> 353
 <211> 321
 <212> DNA
 <213> Homo sapiens

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<400> 353
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<210> 354
 <211> 1422
 <212> DNA
 <213> Homo sapiens

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<400> 354
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<210> 355

<211> 2085

<212> DNA

<213> Homo sapiens

<400> 355

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<210> 356

<211> 2321

<212> DNA

<213> Homo sapiens

<400> 356

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<210> 357

<211> 1747

<212> DNA

<213> Homo sapiens

<400> 357

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<210> 358

<211> 1893

<212> DNA

<213> Homo sapiens

<400> 358

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<210> 359

<211> 2151

<212> DNA

<213> Homo sapiens

<400> 359

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<210> 360

<211> 1107

<212> DNA

<213> Homo sapiens

<400> 360

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<210> 361

<211> 1421

<212> DNA

<213> Homo sapiens

<400> 361

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<210> 362
 <211> 1335
 <212> DNA
 <213> Homo sapiens

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<400> 362
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gttacagaat ggaggttggg aggtagagag gtggaggaag ggtagtggt attgatttct 480
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<210> 363
 <211> 1364
 <212> DNA
 <213> Homo sapiens

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<400> 363
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accacttat acaaaactcag taaacagact ccatcactta atgttttctt gttccctatg 180
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```



```

ccttcacacc ctcagctttt agctaaacat ggatgtatag cccctttttt cctcctcttt 300
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```

<210> 364

<211> 1937

<212> DNA

<213> Homo sapiens

<400> 364

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ataaatgttt aaatgat 1937

```

<210> 365

<211> 1479

<212> DNA

<213> Homo sapiens

<400> 365

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<210> 366

<211> 1408

<212> DNA

<213> Homo sapiens

<400> 366

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```

<210> 367

<211> 1302

<212> DNA

<213> Homo sapiens

<400> 367

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gaaacctgtt gctcttttgc acggaatgtt taaattcaga gttgggatgg gggttgggg 180
gaagcacact tattatcttc agttgcagtg atttcaaatt taggattttt tgttgttgg 240
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```

<210> 368

<211> 1082

<212> DNA

<213> Homo sapiens

<400> 368

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<210> 369

<211> 1119

<212> DNA

<213> Homo sapiens

<400> 369

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<210> 370

<211> 1060

<212> DNA

<213> Homo sapiens

<400> 370

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<210> 371

<211> 3344

<212> DNA

<213> Homo sapiens

<400> 371

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<210> 372

<211> 931

<212> DNA

<213> Homo sapiens

<400> 372

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<210> 373

<211> 1181

<212> DNA

<213> Homo sapiens

<400> 373

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<210> 374

<211> 1336

<212> DNA

<213> Homo sapiens

<400> 374

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<210> 375

<211> 1409

<212> DNA

<213> Homo sapiens

<400> 375

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<210> 376

<211> 1016

<212> DNA

<213> Homo sapiens

<400> 376

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<210> 377

<211> 1528

<212> DNA

<213> Homo sapiens

<400> 377

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<210> 378

<211> 1767

<212> DNA

<213> Homo sapiens

<400> 378

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<210> 379

<211> 1191

<212> DNA

<213> Homo sapiens

<400> 379

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<210> 380

<211> 1187

<212> DNA

<213> Homo sapiens

<400> 380

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<211> 1515

<212> DNA

<213> Homo sapiens

<400> 381

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1515

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2646

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 <211> 1319
 <212> DNA
 <213> Homo sapiens

<400> 383

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<210> 384

<211> 1386

<212> DNA

<213> Homo sapiens

<400> 384

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<210> 385

<211> 2680

<212> DNA

<213> Homo sapiens

<400> 385

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<210> 386

<211> 2076

<212> DNA

<213> Homo sapiens

<400> 386

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<211> 459

<212> DNA

<213> Homo sapiens

<400> 387

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<210> 388

<211> 1341

<212> DNA

<213> Homo sapiens

<400> 388

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<212> DNA

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<212> DNA

<213> Homo sapiens

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<211> 2402

<212> DNA

<213> Homo sapiens

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<211> 1802

<212> DNA

<213> Homo sapiens

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 <213> Homo sapiens

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<211> 1709

<212> DNA

<213> Homo sapiens

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 <213> Homo sapiens

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 <211> 2273
 <212> DNA
 <213> Homo sapiens

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 <212> DNA

<213> Homo sapiens

<400> 411

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<211> 1834

<212> DNA

<213> Homo sapiens

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<210> 413

<211> 1564

<212> DNA

<213> Homo sapiens

<400> 413

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<210> 414

<211> 1191

<212> DNA

<213> Homo sapiens

<400> 414

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<211> 1532

<212> DNA

<213> Homo sapiens

<400> 415

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<210> 416

<211> 1044

<212> DNA

<213> Homo sapiens

<400> 416

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 <211> 372
 <212> DNA
 <213> Homo sapiens

<400> 417
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<210> 418
 <211> 2094
 <212> DNA
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<400> 418
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<210> 419
 <211> 1308
 <212> DNA
 <213> Homo sapiens

<400> 419
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<210> 420

<211> 1792

<212> DNA

<213> Homo sapiens

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<210> 421

<211> 1219

<212> DNA

<213> Homo sapiens

<400> 421

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<211> 2441

<212> DNA

<213> Homo sapiens

<400> 422

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<211> 1510

<212> DNA

<213> Homo sapiens

<400> 423

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<210> 424

<211> 2228

<212> DNA

<213> Homo sapiens

<400> 424

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<210> 425

<211> 1716

<212> DNA

<213> Homo sapiens

<400> 425

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<210> 426

<211> 980

<212> DNA

<213> Homo sapiens

<400> 426

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 <211> 1578
 <212> DNA
 <213> Homo sapiens

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<210> 428
 <211> 1257
 <212> DNA
 <213> Homo sapiens

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<400> 428
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<210> 429

<211> 1151

<212> DNA

<213> Homo sapiens

<400> 429

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<210> 430

<211> 1698

<212> DNA

<213> Homo sapiens

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<210> 431

<211> 571

<212> DNA

<213> Homo sapiens

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<211> 1269

<212> DNA

<213> Homo sapiens

<400> 432

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<211> 1203

<212> DNA

<213> Homo sapiens

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<211> 1207

<212> DNA

<213> Homo sapiens

<400> 434

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<211> 659

<212> DNA

<213> Homo sapiens

<400> 435

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<210> 436

<211> 1070

<212> DNA

<213> Homo sapiens

<400> 436

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<211> 1573

<212> DNA

<213> Homo sapiens

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<211> 2172

<212> DNA

<213> Homo sapiens

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<210> 441

<211> 758

<212> DNA

<213> Homo sapiens

<400> 441

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<210> 442

<211> 1924

<212> DNA

<213> Homo sapiens

<400> 442

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<210> 443

<211> 2169

<212> DNA

<213> Homo sapiens

<400> 443

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<211> 1630

<212> DNA

<213> Homo sapiens

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 <211> 1196
 <212> DNA
 <213> Homo sapiens

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 <211> 1978
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 <213> Homo sapiens

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 <211> 1404
 <212> DNA
 <213> Homo sapiens

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<211> 992
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 <212> DNA
 <213> Homo sapiens

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<210> 451
 <211> 1110
 <212> DNA
 <213> Homo sapiens

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<210> 452
 <211> 1181
 <212> DNA
 <213> Homo sapiens

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<400> 452
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<210> 453
 <211> 1052
 <212> DNA
 <213> Homo sapiens

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<210> 454
 <211> 1637

<212> DNA

<213> Homo sapiens

<400> 454

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<210> 455

<211> 1158

<212> DNA

<213> Homo sapiens

<400> 455

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<210> 456

<211> 2304

<212> DNA

<213> Homo sapiens

<400> 456

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<210> 457

<211> 643

<212> DNA

<213> Homo sapiens

<400> 457

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<210> 458

<211> 2205

<212> DNA

<213> Homo sapiens

<400> 458

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<210> 459

<211> 1251

<212> DNA

<213> Homo sapiens

<400> 459

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<211> 2207

<212> DNA

<213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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<211> 2093

<212> DNA

<213> Homo sapiens

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<210> 467

<211> 1569

<212> DNA

<213> Homo sapiens

<400> 467

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<210> 468
 <211> 1047
 <212> DNA
 <213> Homo sapiens

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<400> 468
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<210> 469
 <211> 1413
 <212> DNA
 <213> Homo sapiens

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<400> 469
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gagagccctc agctgaaaac catggacccc ttctctcctt tgtctaaact caccctcata 240
gtagtctcca aactcctggc tttatgtact atccatatgc tgacaactcc tgcacttaca 300

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1413

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<210> 470
 <211> 955
 <212> DNA
 <213> Homo sapiens

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<210> 471
 <211> 2018
 <212> DNA
 <213> Homo sapiens

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<400> 471
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<210> 472
 <211> 1119
 <212> DNA
 <213> Homo sapiens

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<400> 472
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<210> 473
 <211> 2501
 <212> DNA
 <213> Homo sapiens

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<400> 473
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<210> 474

<211> 2480

<212> DNA

<213> Homo sapiens

<400> 474

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<210> 475
 <211> 1459
 <212> DNA
 <213> Homo sapiens

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<400> 475
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<210> 476
 <211> 1329
 <212> DNA
 <213> Homo sapiens

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<210> 477

<211> 1722

<212> DNA

<213> Homo sapiens

<400> 477

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<210> 478

<211> 2494

<212> DNA

<213> Homo sapiens

<400> 478

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<210> 479
 <211> 1217
 <212> DNA
 <213> Homo sapiens

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<400> 479
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<210> 480
 <211> 2159

<212> DNA
<213> Homo sapiens

<400> 480

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<210> 481
<211> 2208
<212> DNA
<213> Homo sapiens

<400> 481

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<210> 482

<211> 1627

<212> DNA

<213> Homo sapiens

<400> 482

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<210> 483

<211> 1340

<212> DNA

<213> Homo sapiens

<400> 483

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<212> DNA

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<213> Homo sapiens

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<400> 493

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406

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<210> 494
 <211> 939
 <212> DNA
 <213> Homo sapiens

<400> 494

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<210> 495

<211> 629

<212> DNA

<213> Homo sapiens

<400> 495

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 ccagtttaga gattgatgta acagtcccg cagaaagtga tgaggtagct ggggtcggtg 540
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<210> 496

<211> 720

<212> DNA

<213> Homo sapiens

<400> 496

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<210> 497

<211> 511

<212> DNA

<213> Homo sapiens

<400> 497

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<210> 498

<211> 634

<212> DNA

<213> Homo sapiens

<400> 498

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<210> 499

<211> 601

<212> DNA

<213> Homo sapiens

<400> 499

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<210> 500

<211> 773

<212> DNA

<213> Homo sapiens

<400> 500

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<210> 501

<211> 1605

<212> DNA

<213> Homo sapiens

<400> 501

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<210> 502

<211> 1464

<212> DNA

<213> Homo sapiens

<400> 502

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<210> 503

<211> 2174

<212> DNA

<213> Homo sapiens

<400> 503

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<210> 504

<211> 1460

<212> DNA

<213> Homo sapiens

<400> 504

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<210> 505
 <211> 1563
 <212> DNA
 <213> Homo sapiens

<400> 505
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1423

<210> 507

<211> 1576

<212> DNA

<213> Homo sapiens

<400> 507

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1576

<210> 508

<211> 215

<212> DNA

<213> Homo sapiens

<400> 508

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```

215

<210> 509

<211> 1482

<212> DNA

<213> Homo sapiens

<400> 509

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<210> 510

<211> 1403

<212> DNA

<213> Homo sapiens

<400> 510

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<210> 511

<211> 1875

<212> DNA

<213> Homo sapiens

<400> 511

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<210> 512
<211> 1426
<212> DNA
<213> Homo sapiens

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<210> 513
<211> 1617
<212> DNA
<213> Homo sapiens

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<210> 514

<211> 2335

<212> DNA

<213> Homo sapiens

<400> 514

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<210> 515

<211> 1604

<212> DNA

<213> Homo sapiens

<400> 515

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<210> 516

<211> 1345

<212> DNA

<213> Homo sapiens

<400> 516

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<210> 517
<211> 1392
<212> DNA
<213> Homo sapiens

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<400> 517
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<210> 518
<211> 2613
<212> DNA
<213> Homo sapiens

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<400> 518
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<210> 519

<211> 2809

<212> DNA

<213> Homo sapiens

<400> 519

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<210> 520

<211> 516

<212> DNA

<213> Homo sapiens

<400> 520

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<210> 521

<211> 931

<212> DNA

<213> Homo sapiens

<400> 521

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<210> 522

<211> 512

<212> DNA

<213> Homo sapiens

<400> 522

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<210> 523
<211> 875
<212> DNA
<213> Homo sapiens

<400> 523
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<210> 524
<211> 542
<212> DNA
<213> Homo sapiens

<400> 524
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gt 542

<210> 525
<211> 471
<212> DNA
<213> Homo sapiens

<400> 525
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tgtccagcct gggacagtct taaaccccag ggctatagtt agatgtgatg cctttcttgt 180
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tctgaagact tgtatttgag attactctgg catgcttagc atncttttga ctgacttttt 360
caacctccta attgtaatag tagtatctcc gtgtctttgt tctgtttctg gtcagaattt 420
tgccctgganc tgaaaaatat taaagttcac cataaccctt ccagaaaata t 471

<210> 526
<211> 490
<212> DNA
<213> Homo sapiens

<400> 526
cactgaacat tcatacaggga actttcctga agttcagctc aagactaccc tacctgctgt 60

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gtttgtgaga agagtaggat cacacacaca ggtgcaatct tgaccacact tacctgcaag 120
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ttgattcctg                                     490

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<210> 527
 <211> 622
 <212> DNA
 <213> Homo sapiens

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<400> 527
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gccagagtta ttttcttaca ctgttttgca gtggataaag agtgtgattt tgtttgtttg 480
tttgttttga gacagggtct cactctgtct ctctactcaa ggaggctgag gtgggaggat 540
cccttgagtc caggaatttg agattgcagt gggctgtgat cacactactg caccacagcc 600
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<210> 528
 <211> 287
 <212> DNA
 <213> Homo sapiens

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<400> 528
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tccatggaaa gcagctccc aaacaacacc cgcccggtcc gccctccgct gcaactggaa 180
accgcccctg gacgtttctg ccgcagtgct ccctcacgg agttccggtt gtctgcttgg 240
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<210> 529
 <211> 958
 <212> DNA
 <213> Homo sapiens

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<400> 529
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attcttactt ataaagaaac aggtcccaaa actggaaaca gcttagtcca ggctcagcg 180
agaaggaagg acaccatgac tgctccatgc tgggcacagc cgggcagttc tgccaagtgc 240
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<210> 530
 <211> 1583
 <212> DNA

<213> Homo sapiens

<400> 530

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gccaccccc accccttcct ttcagcctcc atcagggaag agacagtaaa aataatcaca 180
gtcaagtgat tcaaaacaaa acaaaaagca actgttaaag ccaagtctgc cccataactt 240
taaaagccat cattgggtcac tgccgatgtc tatttttgaa ggggttgagat ggacagattt 300
cccaagatgc atatcttttg ctttcagttc taacaaatgt tctattagct aaaatgtgtt 360
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caggcatgag ccaccggcgc tggctgggct cgtaattct tatcctagt ccagcttaga 720
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ccaatagacc caaagtctcc aaaaagaagc tcaaggaaga gaaacgaaac aagagcaaaa 1560
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<210> 531

<211> 913

<212> DNA

<213> Homo sapiens

<400> 531

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caccctctcc tgtagggcca gtcagagtct tggtaacaac tacttagcct ggtatcgtca 180
gaaacctggc caggctcccg aactcctcat ccatgtgtt tctaccagg ccaccggcat 240
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ggaacctgaa gactttgcgg tatattactg tcaccaatat actagttcat cgttcaactt 360
tggccagggg accaagggtg tcatcaaaag aactgtggct gcaccatctg tcttcatctt 420
cccgccatct gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgcgtgataa 480
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<210> 532

<211> 703

<212> DNA

<213> Homo sapiens

<400> 532

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tgtggaccag gagccccgtg ggaggaaagt gccctgggg agagctggtg gataccccga 120
atggcaggcc acctggggca aagccagtgg aacctgacta tggcaggatg agaaccacag 180
tgttttataa tgcccacttt tttttcactt cttgcagttt ctatgtttat ttctgttag 240

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catttagtag tatctttatg agtttatctc agttatgcta ggcagaaagg agctcttgtc 300
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gagcacccttg agcgaagtga aatgtgggat ggaaatggaa gctcctgttt gtgatctccc 420
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cagtgaaac catagtgtct gttctgaagt ttgggaaaat agtgtgagac tgtctagctg 660
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<210> 533

<211> 943

<212> DNA

<213> Homo sapiens

<400> 533

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gataattctc tttggtgcgt gcgctgggtg caggaggaaa tatgctaag tagccgtttg 180
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cgcgaaacgg gcaacgggca ggggatcctc cagccaggcg ggcccggggg gtcccgtttc 900
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<210> 534

<211> 520

<212> DNA

<213> Homo sapiens

<400> 534

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ttccagaatt gaaattcaaa tatgtggaag aggagcagcc cgaggagttt tttatccct 180
atgtctggtc tcttgtctac aactcagcag tcggcctgta ctggaatcca caggacatcc 240
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caagcagccc ttcaagttct tttatttctg ggtaacagaa gtagacagac aggttacttg 360
gtgtatcttc tgttaaagag gattgcacga gtgtgttttc ctcacacact ttgatttgga 420
gaattggtgc tagttggcaa tagataactc agcgtagata gtattgcaaa aaggggagga 480
aatacacaac aataataaat gtaaaaacct gccttagaaa 520

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<210> 535

<211> 325

<212> DNA

<213> Homo sapiens

<400> 535

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ggggagtcag tctcgaggac ctcaggggac agccgaagct cccatgacct aaccctaact 60
gaggagggtg tggggctggg cagccgccag ctctctctcag ccgggaggtc tgcggcctgg 120
gcgcccctaa cttcatgtgg ttcttaccgg cagtgggtga gtgtgaagcg tctgccatgc 180
tgccactgga gtgccagtac ttgaacaaaa acgcccgtgac gaccctcgcg ggacccctca 240
ctccccgggt gaagcatttt cagttaaagc ggaacccaa gagcgccacg ctgcgggcgg 300
agctgctgca gaagtgtgag tggcc 325

```

<210> 536

<211> 690

<212> DNA

<213> Homo sapiens

<400> 536

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gcggggagtgc atggcagctc tgggtcccag acctggcccg acccctctgc ttcacctcca 60
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tggtctctcag gcagggtgtac cttgagtcag ccaggagccc tcttttctcg tgtcaaagcc 180
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gggcatggac tgtatcttat gcatctctgt attctctgcg ctagcacggg cctngcacac 660
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```

690

<210> 537

<211> 803

<212> DNA

<213> Homo sapiens

<400> 537

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acatttctct ctoggaacct tgtttactaa ttccactgc ttttaaggcc ctgcactgaa 180
aatgcaagct caggcgccgg tggctcgtgt gacccaacct ggagtcggtc ccggtccggc 240
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803

<210> 538

<211> 419

<212> DNA

<213> Homo sapiens

<400> 538

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gccgccaggt cagcctcagc ctgtgtgatc acagggaaag ttgcgggggg caggggtggtg 360
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<210> 539

<211> 717

<212> DNA

<213> Homo sapiens

<400> 539

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agtctgtaac ggcaggaaag atgaanggga gggctgattt tcgagagccg aatgcagagg 180
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ggttccatcc ctaaacttat acttgcttgt atcatgggat actttgctgg aaaactttct 420

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tatgtgaaaa cttgccaaga gaaattcaag aaacttgaaa attccccct tggagaagct 480
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<210> 540
 <211> 602
 <212> DNA
 <213> Homo sapiens

<400> 540
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 cc 602

<210> 541
 <211> 649
 <212> DNA
 <213> Homo sapiens

<400> 541
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<210> 542
 <211> 545
 <212> DNA
 <213> Homo sapiens

<400> 542
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 ggccctgctc tccctcagcc tctcttcttc tctcctggcc tcttttctgg ggcacctggt 480
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 gcccg 545

<210> 543
 <211> 754
 <212> DNA
 <213> Homo sapiens

<400> 543

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aaaaaatcaa ctgtaataaa gtaattttag tact 754

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<210> 544

<211> 946

<212> DNA

<213> Homo sapiens

<400> 544

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<210> 545

<211> 765

<212> DNA

<213> Homo sapiens

<400> 545

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cacatgccta taatcccagc cctttgggag gtcaagggtg gaggatcgct tgagggcagg 720
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<210> 546

<211> 213

<212> DNA

<213> Homo sapiens

<400> 546

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ggaagccaac agcctccggc cagcagccct acccggggct caacacacag gctgtggctc 180
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<210> 547
 <211> 666
 <212> DNA
 <213> Homo sapiens

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<400> 547
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tgtcttgtcc tcgaagggaat gagtattttg attgtgttca ttaaatctga ttttctatg 660
tcttct                                     666

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<210> 548
 <211> 920
 <212> DNA
 <213> Homo sapiens

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<400> 548
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ttacgccatt gtcttttctc acttctatgc tgtagccaca ccagctgttt ctattcctga 180
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<210> 549
 <211> 707
 <212> DNA
 <213> Homo sapiens

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<400> 549
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gtaaatggta cctctgttga ccccaatgca caggccaaca tcttgcaaat tatccacctt 180
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gggaggctga ggcagaagaa tcacttgagc ctaggaggca gaggttgcag tgagccgaga 660

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ttgcaccact gcactccagc ctgggcaaga aagcgagact ctgtctc

707

<210> 550

<211> 715

<212> DNA

<213> Homo sapiens

<400> 550

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 ctacaaagcc aagaacagga atcacctgat ctccctcagt agacctgata ctgtgagtct 180
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 cctgcacgtt ctatgtcttg gtctgtgtgc acggcaccag cggcagctcc ggggcgcagc 600
 gcggtggcg gccgagcac aggcgtctcg cgaaggccgc gctcccgtg gccgcgcact 660
 cgtaaaaaac gcccccgagc agcgccacgg ccaccaggt gaggggcgcg ggtcg 715

<210> 551

<211> 2163

<212> DNA

<213> Homo sapiens

<400> 551

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<210> 552
 <211> 1783
 <212> DNA
 <213> Homo sapiens

<400> 552
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 tccatatacaa cttattttgt cagcatttga ttttattaaa aattctggac aagaagcatc 420
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 gatggatgta aattggatgt aaatattcag tttatataat tatatcta attgtaacctt 1740
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<210> 553
 <211> 1371
 <212> DNA
 <213> Homo sapiens

<400> 553
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ttgcagtccta ctaaatgtgc aatagcatta tgtctaacaa atatacaaac ctttaatttaa 1260
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<210> 554
 <211> 860
 <212> DNA
 <213> Homo sapiens

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<400> 554
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gctggagtgc agtgggtgtg ccgtgggttt ctgtaacttt gaactagtgg gctgaaggga 780
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aatttttaatt ttttttttcc
860

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<210> 555
 <211> 982
 <212> DNA
 <213> Homo sapiens

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<400> 555
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gctctttttt tttcttctct cttttctttt tttttttttt tttttgtttt tttgtttttt 180
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982

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<210> 556
 <211> 765
 <212> DNA
 <213> Homo sapiens

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<400> 556
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<210> 557
 <211> 845
 <212> DNA
 <213> Homo sapiens

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<400> 557
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<210> 558
 <211> 415
 <212> DNA
 <213> Homo sapiens

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<210> 559
 <211> 722
 <212> DNA
 <213> Homo sapiens

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<400> 559
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<210> 560
 <211> 981

<212> DNA

<213> Homo sapiens

<400> 560

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<210> 561

<211> 826

<212> DNA

<213> Homo sapiens

<400> 561

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<210> 562

<211> 735

<212> DNA

<213> Homo sapiens

<400> 562

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<211> 626

<212> DNA
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<210> 564
<211> 946
<212> DNA
<213> Homo sapiens

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<210> 565
<211> 495
<212> DNA
<213> Homo sapiens

<400> 565
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aaatttattt actcc 495

<210> 566
<211> 302
<212> DNA
<213> Homo sapiens

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gg 302

<210> 567
<211> 580
<212> DNA
<213> Homo sapiens

<400> 567
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<210> 568
<211> 587
<212> DNA
<213> Homo sapiens

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<210> 569
<211> 1788
<212> DNA
<213> Homo sapiens

<400> 569
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<210> 570

<211> 3772

<212> DNA

<213> Homo sapiens

<400> 570

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<210> 571

<211> 1617

<212> DNA

<213> Homo sapiens

<400> 571

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<210> 572

<211> 1616

<212> DNA

<213> Homo sapiens

<400> 572

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<210> 573

<211> 1463

<212> DNA

<213> Homo sapiens

<400> 573

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<210> 574

<211> 2037

<212> DNA

<213> Homo sapiens

<400> 574

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<210> 575

<211> 1434

<212> DNA

<213> Homo sapiens

<400> 575

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<210> 576

<211> 1850

<212> DNA

<213> Homo sapiens

<400> 576

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<210> 577

<211> 1225

<212> DNA

<213> Homo sapiens

<400> 577

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<210> 578

<211> 1589

<212> DNA

<213> Homo sapiens

<400> 578

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<210> 579

<211> 1333

<212> DNA

<213> Homo sapiens

<400> 579

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<210> 580

<211> 1061

<212> DNA

<213> Homo sapiens

<400> 580

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<210> 581

<211> 1634

<212> DNA

<213> Homo sapiens

<400> 581

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<210> 582

<211> 1222

<212> DNA

<213> Homo sapiens

<400> 582

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<210> 583

<211> 1578

<212> DNA

<213> Homo sapiens

<400> 583

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<210> 584

<211> 1951

<212> DNA

<213> Homo sapiens

<400> 584

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<210> 585

<211> 1452

<212> DNA

<213> Homo sapiens

<400> 585

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<210> 586

<211> 1396
 <212> DNA
 <213> Homo sapiens

<400> 586
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<210> 587
 <211> 2047
 <212> DNA
 <213> Homo sapiens

<400> 587
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<211> 1377

<212> DNA

<213> Homo sapiens

<400> 588

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<212> DNA

<213> Homo sapiens

<400> 589

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 <212> DNA
 <213> Homo sapiens

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 <212> DNA
 <213> Homo sapiens

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 <212> DNA
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<210> 594
 <211> 1157
 <212> DNA
 <213> Homo sapiens

<400> 594

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<211> 1590

<212> DNA

<213> Homo sapiens

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<210> 596

<211> 1044

<212> DNA

<213> Homo sapiens

<400> 596

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<210> 597
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 <212> DNA
 <213> Homo sapiens

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<400> 597
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<210> 598
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 <212> DNA
 <213> Homo sapiens

<400> 598

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<210> 599

<211> 1262

<212> DNA

<213> Homo sapiens

<400> 599

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<210> 600

<211> 904

<212> DNA

<213> Homo sapiens

<400> 600

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904

<210> 601

<211> 1048

<212> DNA

<213> Homo sapiens

<400> 601

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1048

<210> 602

<211> 1127

<212> DNA

<213> Homo sapiens

<400> 602

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<212> DNA

<213> Homo sapiens

<400> 603

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<210> 604

<211> 1572

<212> DNA

<213> Homo sapiens

<400> 604

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<210> 605

<211> 1080

<212> DNA

<213> Homo sapiens

<400> 605

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<210> 606

<211> 800

<212> DNA

<213> Homo sapiens

<400> 606

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<210> 607

<211> 1373

<212> DNA

<213> Homo sapiens

<400> 607

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<210> 608
 <211> 1777
 <212> DNA
 <213> Homo sapiens

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<400> 608
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<210> 609
 <211> 2209
 <212> DNA
 <213> Homo sapiens

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<400> 609
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<210> 610

<211> 2054

<212> DNA

<213> Homo sapiens

<400> 610

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<210> 611
<211> 1288
<212> DNA
<213> Homo sapiens

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<400> 611
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<210> 612
<211> 1708
<212> DNA
<213> Homo sapiens

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<400> 612
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<210> 613

<211> 2617

<212> DNA

<213> Homo sapiens

<400> 613

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<210> 614

<211> 595

<212> DNA

<213> Homo sapiens

<400> 614

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<210> 615

<211> 765

<212> DNA

<213> Homo sapiens

<400> 615

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<210> 616

<211> 316

<212> DNA

<213> Homo sapiens

<400> 616

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<210> 617

<211> 1811

<212> DNA

<213> Homo sapiens

<400> 617

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<210> 618

<211> 872

<212> DNA

<213> Homo sapiens

<400> 618

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<210> 619

<211> 1115

<212> DNA

<213> Homo sapiens

<400> 619

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<210> 620
 <211> 1888
 <212> DNA
 <213> Homo sapiens

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<210> 621
 <211> 1903
 <212> DNA
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<210> 622

<211> 1519

<212> DNA

<213> Homo sapiens

<400> 622

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<210> 623

<211> 1014

<212> DNA

<213> Homo sapiens

<400> 623

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<210> 624

<211> 1573

<212> DNA

<213> Homo sapiens

<400> 624

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<210> 625

<211> 1900

<212> DNA

<213> Homo sapiens

<400> 625

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